BRONCHIAL ASTHMA

ITS DIAGNOSIS AND TREATMENT

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PREFACE.

THE greatly increased interest in asthma during the past decade has been attributable, in large part, to the discovery that bronchial asthma is an expression of human hypersensitiveness. The emphasis on this phase of the subject has tended to obscure other important studies that had been done previously. A large bibliography has accumulated, but in no publication in the English language has this been sorted out for the purpose of correlating the older work with the new. In answer to many inquiries as to where one might find such a review, this monograph was undertaken.

The purpose of this book is to present an outline of bronchial asthma. Throughout, an emphasis is placed on the fact that this type of asthma is not a disease entity but a clinical expression of a constitutional defect. The factors which underlie an asthmatic paroxysm are discussed in several chapters. These deal with the anatomical structures which participate in an attack, with fundamental questions of etiology, and with the immunological aspects of asthma. In these chapters, points which have a clinical bearing are stressed. The elaboration of the clinical phases of the subject, however, is dealt with separately in the remainder of the book.

The chapter on treatment is out of proportion to the others in that it dwells at length with the modern methods of therapy. Other than this, the book does not aim at completeness of detail nor are all of the lesser phases of the subject included. There are, however, sufficient references to indicate where information concerning these may be obtained.

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BRONCHIAL ASTHMA.

CHAPTER I.

HISTORICAL CONSIDERATIONS AND DEFINITION OF BRONCHIAL ASTHMA.

HISTORICAL.

The term "asthma" appears in early medical literature, but there was no exactness to its definition at that time. The word is derived from the Greek ἄσθμα which means panting. Bergson[1] elaborately traced the meaning of the word "anguish" in the Book of Exodus, ix: 6, and maintained that it is the first description of asthma. He again found references to asthma in two passages of Homer and in the writings of Herodotus.

Hippocrates[2] did not write specifically about asthma He mentioned it in four of the aphorisms and probably implied it in two others, but there is no evidence that he understood it as a distinct disease Likewise, in the extant works of Galen, there is nothing that identifies asthma as an entity.

Aretaeus[3] who lived, presumably, about 300 A.D., the time of Galen, was the first to record an asthmatic paroxysm and to call it such. His classical description which often is quoted, bears repetition. . . "the evil is much worse in sleep; the voice is liquid without resonance, a desire of much and of cold air. . . They breathe standing as if desiring to draw in all the air which they can possibly inhale; and in their want of air they also open the mouth as if to enjoy the more of it; pale of countenance except the cheeks which are ruddy; sweat is about the forehead and clavicles; the cough is inces-

sant and laborious; the expectoration small, thin, cold, resembling the efflorescence of foam; the neck swells with the inflation of the breath; the precordia is retracted; pulse small, dense, compressed; the legs are slender; and if these symptoms increase they sometimes produce suffocation after the form of epilepsy. But if it takes a favorable turn, the cough is more protracted and rarer; a more copious expectoration of more fluid matter. . . They escape a fatal termination. But during the remissions, although they may walk about erect, they bear traces of the affection."

Celsus[4] who preceded Aretaeus, divided various diseases with shortness of breath into three classes, depending on the degree of difficult respiration, namely, dyspnea, asthma and orthopnea. Despite Aretaeus' exposition of the identity of asthma, the classification of Celsus remained popular into the Middle Ages when asthma was treated more as a symptom than as a definite disease. According to Frank,[5] in the collected works on asthma, more than one hundred bear the title, "Dyspnea, Asthma and Orthopnea." There are many references, also, that associate asthma with organic diseases of the lungs and bronchi. An excellent bibliography of ancient writings on asthma is given by Adams.[6]

In the early seventeenth century, Helmont[7] developed a fanciful theory as to the cause of asthma wherein various "spirits" were involved. Nevertheless, he was the first to suggest that the condition is due to a "drawing together of the smallest terminal bronchi," a theory which since has created endless discussion.

The modern conception of bronchial asthma as a disease entity dates from the writings of Thomas Willis.[8, 9] He identified two forms of asthma; pneumonic, and convulsive. Pneumonic asthma, he associated with obstruction of the bronchi by thick humors, swelling of their walls, and obstruction from without. He believed convulsive asthma to be due to cramps of the muscle fibers of the bronchi, and also of the vessels of the lungs, diaphragm and muscles of the breast.

In 1698, Sir John Floyer[10] published the first edition of his classical book on asthma, and during the next hundred years it reappeared in French, English and German. Its excellence lies in the detail of the clinical description of the disease, of which Floyer himself was a sufferer, and there are many therapeutic suggestions. It had, apparently, a great influence on the English clinicians of the eighteenth century, for Floyer's observations are repeated in many of the books of that period. He adopted Willis' classification of two forms of asthma which he called periodic (convulsive), and continued (pneumonic).

The conception of Willis and of Floyer as to the types of asthma was widely accepted, and reappears in a large English and German bibliography until about the middle of the eighteenth century. There developed, then, a tendency to revert to the ancients and to use the word "asthma" in association with various types of dyspnea and spasmodic afflictions. Thus, many forms of asthma were described under such designations as "asthma humidum," "asthma siccum," "asthma plethoricum," "asthma abdominale," "asthma cardiacum," "asthma arthriticum," "asthma nervosum" and many others. Heberden's[11] angina pectoris which he described at this time, became "asthma pressoriodolorificum," "asthma spastico-arthriticum inconstans," and "asthma convulsivum," according to various authors. There were a few conspicuous observers toward the end of the century who held to the identity of asthma in the sense of Willis, notably Cullen,[12] Withers,[13] Ryan[14] and Bree.[15] Bergson[1] quotes Sauvages (Nostalgia Methodica), Sanger (Systema Morborum) and Wichmann as those who sought also to clarify the existing confusion in nomenclature and by the early nineteenth century, asthma was again considered generally, a convulsive disorder of the bronchi. This result was accomplished largely through the teaching of Cullen who emphasized the role of the nervous system in asthma, and taught that the proximate cause of the disease was pre-

ternatural. He described a spasmodic constriction of the muscular fibers of the bronchi as the immediate cause of the paroxysms. Cullen frequently is cited as the first to expound this theory, although Willis stated it specifically and Helmont suggested it.

A significant contribution to the study of asthma was made by Reissiesen[16] who in 1822 published an atlas on the structure of the lung wherein he demonstrated muscle fibers in the bronchi. This gave credence to the theory of bronchospasm and marked the beginning of much experimental work on this phase of the subject.

At the same time, considerable doubt was being cast upon the theory that the asthmatic attack merely was a functional disorder. This was due, in part, to the observations of Rostan, who, according to Andral,[17] based his opinion on 6 autopsies and declared that asthma was always an affection symptomatic of a lesion of the heart or great vessels. Andral quotes many other physicians of that time who proclaimed an underlying lesion in the circulatory, respiratory or nervous system as a direct cause of the disease. Another factor that tended to confirm this opinion was the discovery of auscultatory methods about this time. Laennec[18] who attributed spasmodic asthma to nervous influences, believed, nevertheless, that these cases were associated with an underlying dry catarrh of the bronchi. Moreover, the development of auscultation frequently revealed defects in the circulatory system and in the lungs of asthmatics not detected by other methods. This controversy gradually subsided with the development of experimentation which showed that asthma could be simulated without organic implication of the viscera.

Although nervous influences had been mentioned frequently as underlying the asthmatic paroxysm, it was not until 1842 that it was demonstrated by Longet[19] that stimulation of the distal end of a cut vagus nerve induced contraction of the bronchi. This led to further experimentation

which will be detailed elsewhere, and it gave great momentum to the theories of "nervous asthma" which were elaborated clinically by Hyde Salter[20] who believed that the lesion of spasmodic asthma resided in the vagus nerve. Salter's book on asthma is remarkable in its comprehension of the clinical aspects of the disease. He described eosinophiles in the sputum before they came to be known as such; he was the first to discuss animal emanations as the cause of paroxysms, and his was the first large compilation of cases.

The latter part of the twentieth century is marked, particularly in Germany, by much physiological experimentation on asthma which led to various theories as to the mechanism underlying the disease. Among these there are two over which there has been much controversy, namely, that the paroxysm is due to bronchospasm, and that it is due to a fluxionary edema of the bronchial mucous membrane. This controversy, as yet, remains undetermined and will be discussed later in this monograph. Clinically, at this time, the treatment of asthma and the frequently associated hay-fever came into the hands of the rhinologists to a considerable extent.

In 1910 Auer and Lewis[21] found that the lungs of guinea-pigs that died in anaphylactic shock became distended because of bronchospasm. Meltzer,[22] on the basis of this observation, pointed out the similarity of the symptoms and lesions to those of bronchial asthma. Wolff-Eisner[23] had already suggested (1906) that hay-fever was anaphylactic in nature. The subject of anaphylaxis then was still new but was receiving a great deal of attention. The application of the skin test to foreign protein substances (which first was demonstrated by Blackley[24] in 1865 in his establishment of pollens as the cause of hay-fever) was being developed by Noon[25] in England and by Cooke,[26, 27] Schloss[28] and Walker[29] in this country. Bronchial asthma came to be considered one of the important clinical expressions of anaphylaxis in man.

The skin test often revealed the underlying cause of attacks and an entirely new approach to the etiology of asthma was thus opened up. The literature on this subject during the past decade is vast, but the clinical conception of bronchial asthma based upon immunological principles is by no means universally understood. This is due to the intricacies of the reactions involved, and also to the fact that immunologists are not of the same mind regarding anaphylaxis and its allied conditions when applied to man.

DEFINITION.

From these historical observations, it will be noted that the word "asthma" has not always been used to designate a particular disease. To the ancients, it implied a degree of dyspnea; in the eighteenth century, it denoted a seizure to which various descriptive adjectives were affixed; and it has been associated with organic lesions. Yet to Aretaeus, Willis, Floyer, Cullen and others, convulsive asthma was a disease entity. In recent years, asthma has come to be looked upon as a symptom, and defined generally as a type of dyspnea accompanied by prolonged expiration and wheezing. When it results, as it does occasionally, from a cardiovascular disorder, it is called "cardiac asthma;" its rare appearance in uremia is spoken of as "renal asthma;" to the wheezing associated with chronic bronchitis, the term "asthmatic bronchitis" is frequently used. It occurs most often, by far, as bronchial asthma, which is a distinct clinical condition and forms the subject of this monograph. This type of asthma is defined by certain criteria which will be considered later. The separation of asthmas with the unfortunate use of the term "bronchial asthma" to denote a particular form has led to much confusion since all asthmas are immediately bronchial in origin. It is one of the entomological failures in medical diction which makes teaching and the conception of the subject difficult.

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CHAPTER II.

ANATOMICAL CONSIDERATIONS.

STRUCTURE OF THE BRONCHI.

It is generally accepted that the symptoms of bronchial asthma, in a large measure, are due to constriction of a part of the bronchial tree. Such a narrowing of the air tubes may be brought about by contraction of muscle fibers in their walls, or by encroachment of the lumina from within by a swollen mucous membrane or by secretions from mucous glands. Before considering the experimental data regarding these possibilities, it is important that the anatomical arrangement and innervation of the bronchi be reviewed.

The right and left main stem bronchi arise from the bifurcation of the trachea near the level of the fourth intervertebral disk and subdivide into three and two main branches respectively, corresponding to the lobes of the lung. Just proximal to this division the bronchi are about 15 mm. in diameter and consist of cartilaginous rings 3 mm. to 4 mm. in width which are incomplete posteriorly and joined to one another by soft tissues. These rings are enveloped in a highly elastic fibrous sheath, continuous with their perichondrium, which further joins them together and also closes their posterior ends and thus completes the tube. Between this sheath and the lumen are the following structures in order: (1) connective tissue containing vascular elements, nerves, and small mucous glands whose ducts pierce the underlying layers; (2) the all-important smooth muscle, the arrangement of which is detailed below; (3) the subepithelial layer made up of loose connective tissue containing blood vessels, nerve filaments and a few lymphoid aggregations; and (4) the epithelium composed of stratified columnar ciliated cells

with a few goblet cells. This arrangement is carried through the larger bronchi. Fig. 1 shows this, although it represents a somewhat smaller tube where the cartilage has begun to fragment.

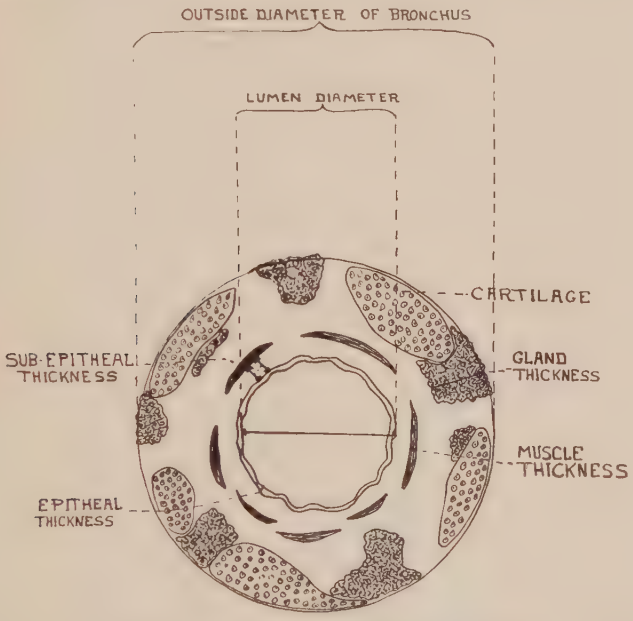

FIG. 1.—Diagrammatic view of the cross-section of a human bronchus. (From Hüber and Koessler.)

As the main bronchi extend downward and outward toward the lower lateral aspect of the lungs, they give off recognizable main and subbranches at fairly wide angles which depend in part upon the degree of pulmonary inflation at the time they are studied. Subdivisions into bronchi of the third, fourth and lesser orders occur with general narrowing of their angles of origin until the branches scarcely can be traced. Whether or not bifurcation is the method of division, is a disputed embryological question. As the lumina of these branches become less than 5 mm. in diameter, the cartilage

begins to fragment, and in the smaller ones it is represented, merely, by scattered angular plaques. It rarely is seen in bronchioles as small as 1 mm. in width. In these smallest elements, the mucous glands, too, disappear and the epithelium flattens out into low cuboidal and finally to squamous form. The mucous membrane here, appears thrown into folds as if squeezed that way by the surrounding smooth muscle.

The structure of the finest bronchioles, especially the disposition of their smooth muscle fibers has been elaborated in a classical demonstration by Miller[2] and deserves attention. He studied the lungs of dogs particularly, as comparative studies showed practically no differences in the arrangement of the muscle layers from those in man. Reconstructions of bronchioles were made from serial sections. The lungs were in the position of full inspiration.

From these models, it is seen that the muscle fibers which, in general, are circularly disposed, are actually in a lattice arrangement (Fig. 2). When the subdivision of the bronchiole *B. R.* is reached, its character changes. Up to this point its walls have been intact, but now alveoli arise from the sides of the tube and the muscle bands form sphincters about their openings. This portion of the bronchiole is the "bronchiolus respiratorious," in contrast to the terminal portion or "ductulus alveolaris" which breaks up into alveoli and forms the anatomical unit (primary lobule) of the lung. These alveoli also are bounded by muscle fibers at their origin from the ductulus alveolaris. All the muscle fibers are confined to the bronchioles; none occur in the alveolar walls. Miller, in measuring muscle thickness at various levels, noted that whereas, for instance, at the lower end of a bronchiole with a diameter of 0.565 mm., the muscle bands measure 0.022 mm. in a ductus alveolaris with a width of 0.192 mm. the muscle measures 0.013 mm. Consequently, while the bronchiole diminished 65 per cent in width, the muscle decreased only 43 per cent in thickness. He mentions Grancher[3] who found

that muscle bands were proportionately five times as strong in a bronchiole 1 mm. in diameter than in a bronchus 10 mm. wide. Miller infers that the network arrangement of the bronchiolar musculature provides the greatest strength as

FIG. 2.—Reconstruction of a bronchiolus with its muscle and its subdivisions from the lung of a dog. (Courtesy of Prof. William Snow Miller.) *B.R.*, Bronchiolus respiratorius. *D.A.*, Ductulus alveolaris. *A.*, Atria. *S.A.*, Air sacs.

well as the widest excursions during respiration. He believes further, that these muscles take an active rather than a passive part in respiration by facilitating the expulsion of air. This has not been proved.

INNERVATION.

This demonstration of muscle fibers whose action causes bronchoconstriction without an opposing group to pull them open, invites a consideration of the innervation of these structures. It has been amply demonstrated that bronchoconstriction occurs on stimulation of the vagus nerves which are the only motor pathways to the bronchial muscles. (See Chapter III). Marked contraction can occur only in the smaller bronchi devoid of adequate cartilaginous support. The vagus represents the autonomic portion of the vegetative nervous system, the opposing fibers being those of the spinal sympathetics. Structures controlled by the vegetative nervous system have a dual or antagonistic innervation. Consequently, after bronchoconstriction occurs from vagus stimulation, relaxation takes place on stimulation of the sympathetics or by vagus release. This is nicely demonstrated in bronchial asthma wherein contraction of the bronchial musculature presumably is responsible, at least in part, for the paroxysm. This is terminated almost immediately after an injection of epinephrine which acts specifically as a stimulant to the sympathetic fibers. Constriction ceases, not from the pull of an opposing set of muscles but from effective vagus inhibition brought about through the antagonistic action of the sympathetics. Consequently, the constrictor muscles merely relax, although there may be a temporary loss of tonus, and the bronchi widen. Möllgaard[4] and others[5, 6] have assumed special bronchodilator mechanisms, and Weber[7] believed that a bronchodilator center exists in the spinal cord, but sufficient proof of these is lacking.

The vagus fibers which serve the lungs, descending from the vagus nuclei and the sympathetic fibers from the superior and middle cervical ganglia, also going to the lungs, meet in the anterior and posterior pulmonary plexuses where they become closely interwoven. Then, they travel into the lungs where they soon become differentiated into three systems of

plexuses bronchial, vascular, and pleural. Crossing of some of these fibers exists. Weber[7] has shown that stimulation of the peripheral stump of a cut vagus on one side will give bronchoconstriction in both lungs although this is more marked on the cut side. On the other hand, according to Dixon and Brodie,[6] bronchoconstrictor fibers have a unilateral distribution only, but this is not probable.

The bronchial fibers from the pulmonary plexuses run in the bronchial walls and are disposed into two groups which anastomose. One lies external to the cartilage and the other between the cartilage and smooth muscle. (Larsell[8, 9, 10]). The latter or subchondral plexus distributes fibers to the muscle, mucous glands and epithelium and contains motor, secretory, sensory and inhibitory filaments. In the smaller bronchioles, both plexuses intermingle. Müller,[11] by special preparations, has demonstrated minute multipolar ganglia distributed among the bronchial fibers, but their significance is not understood.

Although there is ample experimental proof that motor fibers in the vagus cause bronchoconstriction, there is no direct evidence concerning the mechanism of secretion from the mucous glands. Histologically, fibers from the bronchial plexus can be traced to these structures and it is inferred, therefore, that some are secretory and others inhibitory, as no nerve elements other than those of the vegetative nervous system are known in the bronchial plexuses Whether the secretory fibers are vagus or sympathetic has not been established. In the glands of the upper respiratory tract they may be either. Although animal experimentation is lacking here, bronchial asthma offers suggestive evidence. As will be shown (Chapter III) there is every reason to believe that during an asthmatic paroxysm, bronchoconstriction from vagus stimulation occurs. Abundant mucus secretion is produced immediately after an attack when, presumably, it is released from the relaxed bronchi. It may be argued that sympathetic stimulation which relaxes bronchospasm,

at the same time stimulates the mucous glands and thus mucus is coughed up at the end of an attack. This is refuted, however, by bronchoscopic observations during paroxysms when large collections of mucus were observed.[12] On such grounds, it is believed that mucus secretion is induced by peripheral vagus stimulation. As the mucous glands are found only in the larger bronchi, then bronchial asthma involves not only the smaller air tubes, but a large portion of the bronchial tree.

Sensory fibers from the bronchial plexus form a rich network in the bronchial epithelium which accounts for the fact that the mucosum is very sensitive to mechanical stimuli. This irritability serves to protect the vital respiratory mechanism in the alveoli against foreign matter. This fact has an important bearing in bronchial asthma wherein the bronchial mucosum is notoriously hyperirritable. Such benign stimuli as cold air, wind, rapid breathing and even laughter may induce a paroxysm. In these cases the reflex pathway is *via* the ascending fibers of the vagus to the vagus nuclei and thence down the motor fibers to the peripheral structures.

The bronchial vessels arise largely from the systemic vasculature - the bronchial artery is a branch of the aorta—and anastomose with the pulmonary system.[13] They run along the outer walls of the bronchi with terminal distributions in the muscles, glands and mucosa (subepithelial layer). Their vasomotor control is established by a separate nerve plexus (the vascular division of the pulmonary plexuses). The systemic arteries have vasoconstrictor and vasodilator fibers from the sympathetic and parasympathetic (vagus) portions of the vegetative nervous system, respectively, and this innervation is carried into the bronchial vasculature.[8] Whether or not the pulmonary vessels, with which this anastomoses, have vasomotor fibers, is still a matter of dispute, although, in all probability, vasoconstrictor fibers, at least, are present.

It is seen, therefore, that the bronchi are entirely under the control of the vegetative nervous system. Distal stimulation of the vagus portion causes contraction of the bronchial muscles, a dilatation of at least a part of the bronchial vessels and probably secretion from the mucous glands, as well as inhibitory influences on sympathetic stimulation. On the other hand, sympathetic stimulation inhibits vagus pull with consequent relaxation of constricted bronchial muscles, vasoconstriction and probably it inhibits mucus secretion. The clinical significance of these effects will be elaborated in succeeding chapters.

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CHAPTER III.

PATHOGENESIS OF BRONCHIAL ASTHMA.

The experimental study of asthma is handicapped by two things. In the first place, bronchial asthma is essentially a disease of man. Although the paroxysmal attack may be simulated both experimentally and spontaneously in animals, in both cases many of the underlying features of the disease are lacking. Such studies, however, have led to much of our knowledge concerning the physiology of the bronchi. Again, death as a direct result of bronchial asthma is very rare, and, consequently, little postmortem material has been available for study. It is, indeed, surprising how extremely few physiological observations on man have been made, other than immunological studies.

There are two distinct phases of the etiology of bronchial asthma. The first is that of the mechanism of the asthmatic paroxysm, and the second, the underlying factors which initiate this mechanism. These will be treated separately.

THE MECHANISM OF THE ASTHMATIC PAROXYSM.

Theory of Bronchospasm.—The oldest theory of the immediate cause of an asthmatic attack deals with a convulsive spasm of the bronchi. This theory had its origin in the observation by Willis that there were no lesions in the lungs of 2 cases of spasmodic cough. One of these patients who died in an attack of asthma was not seen by Willis but he received this information from the learned physician Walter Needham. The other was a child, aged twelve months, an epileptic, who was "often taken with cruel sobbing or whooping cough." This theory of bronchospasm was reasserted by many subsequent authors although the muscles in the

bronchi were not discovered until almost a century and a half after Willis' publications. Willis probably believed that he saw muscle tissue in the bronchial walls.

The earliest experimental work on bronchospasm recorded the simple observation that the lungs have the power to contract. Haller[1] in 1756 noticed the lung draw itself together on the application of concentrated acid but noted no contraction of the bronchi when they were irritated directly. Varnier[2] in 1779 reported that the finer air tubes of the lungs contracted on the application of fumes, irritating liquids and from mechanical irritation. Prochaska[3] (1802) noted that the lungs of an animal whose thorax was opened during life contracted to a greater degree than those of a dead animal and he assumed thereby inherent contractile elements other than elastic tissue. Some years later Wedemeyer[4] described a narrowing of the finer bronchioles, those with a diameter of 0.5 mm. to 1 mm., on the application of mechanical or of galvanic stimuli. These bronchioles became so narrowed that some become obliterated. The larger tubes showed no such effect.

Williams[5] (1840) usually is credited with having been the first to demonstrate bronchial contractility. He showed this by removing the lungs of a pithed dog and tying a bent tube like an inverted siphon into the trachea. This tube contained a colored liquid. On passing a galvanic current from the margin of the lung to the brass tube in the trachea, the fluid rose nearly 2 inches, and sank on breaking the contact. He did many such experiments, applying stimuli to the trachea, lungs, vagus, etc., and concluded therefrom that the air tubes are possessed of irritable contractility. The contractility, however, resembled that of the intestines rather than voluntary muscle. It is interesting that Williams was unable to produce this effect by stimulating the nerves to the lungs. It occurred only through contact with lung tissue.

About this time, Budd[6] performed similar experiments, but was unable to produce bronchial contraction. He used a

very strong current, however, which caused necrosis of tissue at the point of contact, Budd concluded that the transverse fibers of the bronchi had been supposed incorrectly to be muscle tissue.

Although up to this time considerable experimentation on the influence of the vagus nerve on respiration had been done, the innervation of the bronchial musculature had not become established. Longet solved this problem by the simple expedient of using large animals. On stimulating the peripheral end of a divided vagus of a horse and an ox, he observed marked contractions of the musculature of the bronchi in resected lungs, especially those of very fine caliber. This important physiological observation opened up a broad field of research.

Volkmann[7] was unable actually to see bronchial muscle contraction in dogs but he ingeniously demonstrated it in another way. He bound a little tube in the trachea of a decerebrate dog. He then held a flame near the tube and on stimulating the vagus the flame became dim and, in one experiment, was blown out, thus demonstrating increased tracheal pressure.

Volkmann's experiment was repeated in subsequent years with improved experimental methods and led to much discussion. Donders[8] used a manometer and claimed that Volkmann's conclusions were erroneous. However, Donders stimulated the vagus but five times and actually did get some rise in pressure, but he attributed this to a contraction of the thoracic muscles. Paul Bert[9] in 1870 devised a specially constructed manometer and used a fresh lung-vagus preparation free from other viscera. On stimulating the vagus stump galvanically, he recorded graphically, a rise in intratracheal pressure,

There was considerable experimentation in this direction at this time, notably by Töpelitz[10] and Rügenberg[11] but nothing significant was accomplished until 1876 when Gerlach[12] introduced the use of curarized animals. Until then, dead

preparations had been largely employed. Curarization allowed the simultaneous measurement of intratracheal, intrapleural and circulatory pressures, but it also introduced many extraneous influences which had to be controlled. Gerlach by adjusting his current, believed that he demonstrated bronchial contraction on distal vagus stimulation. These experiments were repeated soon after by MacGillavry,[13] Riegel and Edinger[14] and by Brown[15] who believed that the vagus carried both constrictor and dilator fibers to the bronchi.

Sandmann[16] (1890) by using an elaborate apparatus, likewise obtained a rise in intratracheal pressure on vagus stimulation. He pointed out, however, the difficulty of interpreting such a result, in that vagus stimulation causes a change in heart rhythm and in blood-pressure and these two lead to alteration of the blood content of the thorax. This alteration in itself would increase pressure in the air tubes. He concluded that weak induction currents narrowed the bronchi and strong ones dilated them. He found, also, that nasal stimulation caused bronchospasm. On cutting both vagi, this spasm was inhibited.

Beer[17] in 1892 reconsidered the problem of vagus stimulation, and pointed out the probable technical errors of other investigators. He paid scrupulous attention to the standardization of his experiments and took intracardiac, intrapleural and intratracheal pressures simultaneously. On stimulation of the distal vagus stump of a dog there was a constant rise of intratracheal pressure. There also was cardiac standstill in diastole and the consequent possibility of increased blood volume in the lung. The influence of circulatory factors were controlled by repeating the experiment on a dead animal with the heart severed. Beer concluded that bronchospasm was the essential factor in his results. He commented also upon lung inflation and the consequent passive descent of the diaphragm which he attributed to air trapped by the narrowed bronchi.

Einthoven,[18] in the same year, improved the experiment by providing a constant volume of air at a given pressure that was inhaled with each breath. The strength and duration of the electrical current likewise were controlled. He used a large number of dogs and found, without exception, that they showed a rise of intratracheal pressure on stimulation of the peripheral stumps of one or both vagi. Circulatory factors were controlled carefully, and Einthoven concluded they were of little importance and that bronchospasm played the essential role. He stimulated the central vagus stump but found no evidence of active bronchodilatation which Brown and others had asserted would occur. Einthoven found, further, that bronchospasm finally relaxed because of muscle fatigue. This fact had been noted by Williams, and it may explain the gradual cessation of asthmatic paroxysms.

At this time there was an active opposition to the theory of bronchospasm, particularly by Basch[19] and his pupils who contended that circulatory forces were the essential factors in raising intrapulmonic pressure on vagus stimulation. Basch criticized Einthoven's work on the ground that blood-pressure was taken from the carotid rather than from the left auricle which, he contended, would reveal an increased pressure of the pulmonary circulation on vagus stimulation. This would result in a narrowing of the bronchi from congestion of the bronchial vessels and lead to the increased intratracheal pressure which Einthoven recorded. Grossmann[20] performed a large number of experiments, and took intracardiac as well as systemic blood-pressures. He found that vagus stimulation caused a fall in systemic pressure and a rise in that of the pulmonary circuit. Grossmann concluded therefrom, that under these conditions, a rise in intratracheal pressure was due essentially to overfilling of the lung capillaries, and that bronchospasm was unimportant.

Brodie and Dixon[21, 22] devised a lung oncometer which would record the volume of isolated lobes. They stimulated

the vagus and measured the resultant tracheal pressure, lung volume and aortic pressure. They found not only bronchoconstriction, but an actual reduction of the blood content of the lung. This they assumed from a rise in intratracheal pressure with a simultaneous decrease in lung volume. To exclude vascular effects, a control excitation was made, and again after the animal was bled to death. In each instance, the effects of bronchospasm were recorded. Brodie and Dixon showed, moreover, that simulation of the posterior portion of the nasal mucous membrane induced the same effect which was abolished when the vagi were severed. They believed, also, that they found the presence of bronchodilator fibers in the vagus. This seemed plausible, for Aufrecht[23] had just demonstrated anatomical preparations which he represented as longitudinal (dilator) fibers in the bronchial musculature. According to the late work of Miller, Aufrecht misinterpreted these fibers.

Strümpell[24] (1908) in discussing the mechanism of asthma did not believe the theory of bronchospasm proven. He remarked that the best proof of this would be if one could observe definite hypertrophy of the bronchial muscles in an anatomical investigation in cases of chronic asthma. He knew of no such study. It is noteworthy that Hüber and Koessler in 1922 made just this observation from their careful measurements of bronchial muscle tissue in a series of asthmatics.

Auer and Lewis investigated the immediate cause of death in anaphylactic shock. They worked with guinea-pigs and found that asphyxia, also lung inflation, occurred secondary to bronchospasm. This could not be prevented by section of the vagi or by destruction of the spinal cord and medulla, and hence is a peripheral effect. Since atropine has been found to prevent contraction of smooth muscle from sensitized guinea-pigs, when brought in contact with the specific antigen with which the animals had been injected[25] it appears likely that anaphylactic poison works on vagus nerve endings, although Gasser[26] has pointed out that atropine may act upon smooth muscle tissue itself.

Cloetta[27] and Fröhlich and Pick[28] produced bronchospasm by the use of pilocarpine, which stimulates vagus nerve endings, and by hypophyseal preparations. This could be prevented by atropine but not by cutting the vagi.

Weber[29] (1914) modified Brodie and Dixon's oncometer method, so that two lung lobes could be exposed at the same time. This gave comparative effects of both circulatory and bronchoconstrictor influences. He used 150 animals, mostly cats, and proved that bronchial constriction played the important role. Weber showed, likewise, that stimulation of the vagus on one side acted on the bronchial muscles of the opposite lung, but to a lesser degree.

From these experiments and many others which confirm them, it may be inferred that bronchospasm occurs when stimulation is applied to the efferent fibers of the vagus nerve trunk or to the vagus nerve endings in the bronchial musculature. Stimulation of the central end of a cut vagus has been found to produce bronchospasm also, in some instances, but the pathways are so difficult to trace that they cannot be assumed to be due to vagus influence alone. Not only does bronchospasm occur under the above conditions, but in the living animal there is consequent lung inflation also. That circulatory effects outside of the bronchial walls contribute toward narrowing the air tubes, is doubtful. In spite of this evidence such a competent authority on this subject as Coca[30] maintains that the theory of bronchospasm is not proven, and that the lesion of asthma is an edema of the bronchial mucosa.

Theory of Mucosal Edema. The theory of mucosal edema as a cause of bronchial narrowing is of much more recent origin than that of smooth muscle contraction, and there is considerable evidence in favor of its occurrence. Beau[31] in 1848 was the first to suggest this. He developed a method of clinical distinction between various forms of bronchitis based on auscultation. From the character of the rales and the sputum in asthma, he assumed that there was a mucosal

swelling (as in inflammatory bronchitis) and blockage of the smaller bronchi by secretion. Similar deductions were made by Bretonneau,[32] Villemin[33] and Biermer.[34]

In 1865, Blackley, in establishing the fact that pollens are the cause of hay-fever, made an observation which came to have great importance in later years. He found that when certain pollens were rubbed into the abraded skin of hay-fever subjects, a local edema developed (the typical positive skin reaction). He observed also an edema of the nasal mucosa in these individuals on the application of such pollens. Inasmuch as bronchial asthma frequently is associated with pollinosis, it became a fair inference that the bronchial lesion was also a mucosal edema. Strümpell,[24] Sihle,[35] Solis-Cohen[36] and others developed this thought further. They noted that urticaria and angioneurotic edema which are often associated with bronchial asthma were caused by localized edema, and they suggested that the lesion was the same in all—a localized swelling.

Curschmann[37] (1883) who described spirals that are identified with his name, in the sputum of asthmatics, believed that these came from the finer bronchi and that they represented an exudative process therein. He argued that the initial lesion of bronchial asthma is a swelling of the bronchial mucosa which give off an exudate. This in turn plugs the finer tubes and then bronchospasm is induced reflexly, which compresses the exudate into spiral forms.

The extensive work of Grossmann and Basch who contended that circulatory effects in the lungs and bronchi with subsequent swelling of the mucous membranes are responsible for the asthmatic paroxysm, has been noted above.

More direct evidence that swelling of the bronchial mucosa occurs during an asthmatic paroxysm is found in postmortem sections. This has been noted by Fraenkel,[38] Jezierski,[39] Faschingbauer,[40] and others although it has not been a constant finding. The difficulties in the interpretation of such sections are many. Some of the cases reported were prob-

ably not true bronchial asthma; desquamated epithelial cells upon which emphasis has been laid, may have been a postmortem effect; and it is difficult to estimate lesions in the mucosa when it is folded by bronchospasm and thus thickened.

The similarity of pathological sections of the lungs of guinea-pigs that died in anaphylactic shock, to those of bronchial asthma has been noted by various observers. Storm van Leeuwen[41] and his associates induced asthma-like symptoms in guinea-pigs by inhalation methods. Some of these animals died in anaphylactic shock and showed markedly congested bronchi. Busson and Ogata[42] performed similar experiments with like findings. Schmitt and Barth[43] tied off the right common carotid artery in guinea-pigs. They then injected anaphylatoxin agar into the central stump and produced typical anaphylactic shock. In another series, agar was injected into the peripheral stump and no symptoms occurred. On intravenous injection there were mild symptoms. They inferred from these experiments that the site of symptoms were the bronchial vessels which anastomose with the alveolar vessels and thus received the toxic material. As a result of this vacular endothelial stimulation, an edema of the mucous membrane resulted. They reported no pathological investigation, however, to confirm their conclusion.

The best evidence that an edema of the bronchial mucous membranes occurs during an asthmatic paroxysm is reported in bronchoscopic findings. Pieniazek[44] apparently was the first to make direct bronchoscopic observation during an asthmatic attack. This was in a child, aged two and a half years. The instrument was passed into both bronchi and the mucous membrane was found intensely red and swollen. Nowotny[45] reported another case of typical bronchial asthma in which hyperemia and swelling of the mucous membrane during an attack were seen as far down as the bronchi of the second order. These conditions quickly disappeared after

the application of cocaine and epinephrine. The same patient was examined when not in an attack, and no edema was found. Yankauer[46] asserted that the examination of the bronchi during an attack of spasmodic asthma shows that the mucous membrane is congested and that the lumen of the bronchi is narrowed further by contraction of the muscular coat. Keiper[47] and Galebsky[48] made similar observations. Freudenthal[49] emphasized the large collections of mucus seen during attacks, but said little concerning mucosal edema. Ephriam[50] in 1912 criticized bronchoscopic reports in asthma previous to that time, insofar as the bronchial mucous membranes were concerned. He stated that unless the instrument were passed very gently, straining from cough or gagging would redden mucosal tissue before a good observation could be made. Ephriam observed hyperemic bronchial walls during an asthmatic paroxysm, and then, with the instrument in place, saw blanching after the subcutaneous injection of epinephrine.

Some of these observers did not find bronchial edema in all cases, but the effect of the local anesthetic was not always considered; and some cases evidently suffered from chronic bronchitis and not from asthma. Although the finer bronchi which presumably are the chief site of the lesions in an asthmatic paroxysm are far from the limits of bronchoscopic vision, nevertheless there is every reason to believe that mucosal swelling extends throughout the bronchial tree during an attack. Just such an edema is a common finding in the nasal mucous membrane during asthma. The lower portion of the tract doubtless is affected likewise, an assumption strengthened by pathological findings. Sections of mucosa taken from each of these sites in a case that died soon after an attack were found to be very similar (see Chapter IV).

There is much, therefore, to substantiate the theory of mucosal edema as an immediate cause of the asthmatic paroxysm. Whether this, or whether bronchospasm be the sole factor or, at least, the dominant one, has been a

matter of controversy for the past forty or more years. It has been suggested that both may occur (Chapter II), and this invites again the consideration whether each may be initiated by the same stimulus.

Grimm[51] infers that inasmuch as striated muscle during work requires an increased blood supply, the same thing must apply to smooth muscle and that this would lead to a hyperemia of the bronchial tissues. Although such hyperemia may not contribute greatly to bronchial narrowing, it indicates, at least, that both processes may occur simultaneously.

The bronchial vessels are derived from the systemic vasculature but anastomose freely with those of the pulmonic system, especially in the finer bronchioles. The vasomotor innervation of the systemic vessels is supplied by the vegetative nervous system which likewise innervates the bronchial musculature (Müller[52]). Vasoconstriction occurs on stimulation of the sympathetic fibers, and relaxation is produced on excitation of the parasympathetic (vagus) fibers. (Whether the same effect takes place in the pulmonary vessels is a matter of dispute. Plumier[53] and Campbell[54] observed vasoconstriction on sympathetic stimulation with epinephrine, but this has been refuted by Mellin[55] and Hallion.[56])

It is quite probable, therefore, that peripheral stimulation of vagus fibers going to the lungs causes both bronchoconstriction and vasodilatation of at least a portion of the bronchial vessels. As discussed in Chapter II, the same stimulus that induces such bronchospasm and mucosal edema may cause mucus secretion as well, so that all would occur simultaneously. If this be so, there is no ground for controversy as to which of these is primarily the immediate cause of an asthmatic paroxysm.

If vagus stimulation initiates the mechanism that brings on asthmatic breathing, and this is the only theory with sufficient experimental data to substantiate it, then the question arises as to which portion of the vagus becomes

stimulated. It will be seen later in this chapter that in an asthmatic individual, there are many things that may cause an attack. For instance, psychic factors, nasal manipulation, and the inhalation of volatile substances, may all be responsible for setting off a paroxysm. The first may be accounted for by central vagus stimulation, the second by stimulation of the vagus reflexly through its nasal connections, and the third by irritation of the nerve endings. The separation of these factors as well as opinions based solely upon isolated clinical examples, has led to much of the existing confusion about asthma. Thus, much has been written about "nervous asthma" and treatment of the disease has been directed largely through psychotherapy; "nasal asthma" forms a large bibliography and a great deal has been promised from nasal surgery alone; and "allergic asthma" wherein the inhalation of foreign protein substances is responsible for most cases, is much in vogue.

Other Theories of Mechanism.—With a conception of the probable mechanism of the asthmatic paroxysm, the various underlying influences which may initiate this will be considered. It may be well, however, to mention a few of the many other theories concerning the mechanism of an attack, some by reason of their historical interest, and others because they still receive serious consideration.

Wintrich[57] in 1854 stated that asthma was due to a tonic spasm of the diaphragm. He believed that the expiratory forces were far greater than bronchospasm could withstand, and that such a spasm would account for lung inflation. Wintrich based his opinion on the results of animal experimentation and it was substantiated by other observers.[14, 58] This theory was considered seriously for many years until entirely refuted by radioscopic observations.

The theory that asthma is due essentially to an underlying infection of the respiratory tract has always received much support. It was believed by the ancients and it established the "asthma sec" of Laennec. A large literature deals with

the association of bronchitis and asthma from which the term "asthmatic bronchitis" evolved. Pulmonary tuberculosis has been named the cause of asthma by many, and on the other hand it has been pointed out by others that the two conditions seldom coexist. That tonsil infection, tooth infection, and sinus infection inducing bronchitis and, consequently, asthma play important roles has been stated repeatedly, especially by rhinologists. There is little experimental evidence that infection anywhere directly induces an asthmatic paroxysm excepting in cases of rhinitis and bronchitis wherein vagus fibers or their connections are exposed to the lesion and thus irritated. The underlying influence of infection in asthmatics may be great, however, and will be considered subsequently.

A great deal of attention has been given to the theory that an asthmatic paroxysm is due directly to nasal irritation. Of importance, are the observations that stimulation of parts of the nasal mucosa may induce bronchospasm in animals; likewise the discovery of asthmogenic areas in the human nose, irritation of which may cause attacks in those afflicted with the disease. François Franck[59] was the first to report that electrical and mechanical stimulation of the nasal mucous membrane of dogs induced bronchospasm. Lazarus,[60] Sandmann[16] and Brodie and Dixon[21] observed the same thing. The reaction was inhibited entirely after severing both vagus nerves. The points of stimulation in the nose which give bronchospasm have not been fixed. Franck stated that the anterior tip and free border of the middle and inferior turbinate are the most sensitive parts. Sandmann included the posterior portion of the septum. Killian[61] located these in man, at the tuberculum septi and at the anterior and posterior tips of the inferior turbinate. Sluder[62, 63] made an important contribution by demonstrating that cocainization of the nasal (sphenopalatine) ganglion, or its injection with alcohol would at times terminate an asthmatic paroxysm, and in some of his cases he thereby prevented a recurrence. This has been substantially confirmed.

All of these observations point to a nervous pathway from the nose to the peripheral bronchial fibers of the vagus, but this has not been satisfactorily traced. Hazeltine[64] assumes that sensory impulses arise in either the ophthalmic or the superior maxillary division of the trigeminus, either with or without a relationship to the sphenopalatine ganglion; then through the sensory root of the trigeminus and by means of collateral neurones a synaptic relationship is established with the motor neurones of the vagus nucleus. This, in turn, sends efferent impulses to the musculature of the respiratory passages. Hazeltine elaborates this contention at length, but this pathway has not been worked out experimentally as one that in asthmatics carries impulses from the nose, that result in bronchospasm. However, a pathway undoubtedly exists, and cocainization of the sphenopalatine ganglion would serve to block impulses which arise in cases of nasal irritation, but would have no influence when a paroxysm develops from stimulation of vagus nerve endings in the bronchi. It is entirely probable, then, that polyps or inflammatory processes in the nose may be important factors which are responsible for asthmatic attacks.

There are other theories concerning the mechanism of a paroxysm which deal with laryngeal spasm (Talma[65]), spasm of the pharyngeal muscles, (Brügelmann[66]) congestion of the alveolar capillaries (Winter[67]) and the "non-passive respiration" theory of Brown[68] wherein straining from forced expiration causes pulmonic vascular engorgement. These have not received confirmation.

FACTORS WHICH INITIATE A PAROXYSM.

Psychic and Nervous Influences.—Since stimulation of the vagus nerve may be central, truncal or peripheral, the factors causing such stimulation will be considered.

Little is known concerning impulses which are carried to the vagus nuclei excepting those that travel up the sensory fibers of the vagus trunks. On the other hand, there is no

doubt that psychic factors are sometimes directly responsible for asthmatic paroxysms of which some classical examples have been described.[69, 70, 71] Not long ago, asthma was thought to be due essentially to a psychoneurosis (Treüpel,[72] Alvellis,[73] Saenger[74]) but this theory no longer has much support. Grimm[75] points to the analogy of the presumed etiology of most gastro-intestinal disturbances which were believed to be psychic at one time. Pescatore,[76] commenting upon the theory of psychic asthma, inquires why it is that infants have their asthma particularly at the time of their eczema and whether this be a Freudian phenomenon. He notes, also, the absence of asthma in other psychical disorders. Yet, one does see asthmatics occasionally, whose attacks are influenced, without doubt, by emotional disturbances. These examples are few, however, and it may be that these patients are essentially psychoneurotic. The explanation of asthmatic attacks in relation to their psychosis is merely conjectural. Schwab[77] believes that certain individuals with emotional disorders seek an outlet for these and that pathways already established are the most available. If they be chronic asthmatics, the vagus nuclei could be involved in the reaction, and a paroxysm set off.

Although the theory that asthma is due to a psychosis has been limited, nevertheless the contention that asthma is a nervous disorder, is age-long, and has been popular both among physicians and among the laity. There is little doubt that many asthmatics are of a nervous disposition. Lord[78] suggests that the so-called "neuropathic constitution" found in asthmatics may well be caused by asthma rather than precede it. The constant apprehension of an attack, the loss of sleep and the hopelessness of permanent relief; these things in themselves affect the nervous system. This explanation is hardly adequate, as many patients trace their nervousness to a period long before their paroxysms.

In 1909, Eppinger and Hess[79] emphasized the importance of the vegetative (involuntary) nervous system in certain

clinical conditions. They considered separately the two component parts of this system, the sympathetic, and the parasympathetic (vagus) elements. Since organs which are innervated by this system receive fibers from both portions, they contended that normally, impulses from each keep the other in balance. If, however, the "pull" of one system becomes greater than that of the other, it gives rise to symptoms depending on the organs affected. They based their contention on pharmacological experiments with pilocarpine and epinephrine. In small doses, these cause no symptoms in normal individuals. In cases of vegetative nervous system imbalance, they cause exaggerated response, depending largely upon which portion of the system is dominant. Thus, with increased vagus tone, or vagotonia, small doses of pilocarpine which stimulates vagus nerve endings will give symptoms referable to the vagus; a feeling of warmth, flushing, sweating; also bradycardia and, in asthmatics, paroxysmal attacks. Eppinger and Hess contended that certain clinical conditions could be explained by such vagotonia, of which they considered bronchial asthma the best example. They believed that individuals with such imbalance were either vagotonic or sympathicotonic, but not both. These observations soon were confirmed by Barker and Sladen,[80] and Falta,[81] and this important new field of study has since received much attention. It was found subsequently by Petren and Thorling,[82] and by Wilson[83] that certain individuals may give exaggerated responses both to pilocarpine and epinephrine (Eppinger and Hess later recognized this) and thus there may be a heightened irritability of both elements of the vegetative nervous system. Alexander and Paddock[84] tested a series of bronchial asthmatics and found just this response. Herein lies a rational explanation for the nervous temperament of patients with asthma, for most conditions of dual imbalance (dystonia) are associated with nervous manifestations (laryngospasm, gastrospasm, hyperthyroidism, etc.).

Although stimulation of the vagus trunk has been the principal way of demonstrating bronchospasm in animals, clinically such stimulation probably does not exist.

Stimulation of Vagus Nerve Endings.—There remain to be considered the factors which stimulate vagus nerve endings. Of these, there are two groups; those which act on the sensory fibers of the vagus, and those which irritate the motor and probably the secretory fibers directly. Concerning the first group, it is common knowledge that chronic asthmatics may have attacks from mechanical stimulation of the bronchial mucous membrane which apparently becomes very irritable. The inhalation of dust, fumes, cold air, steam, and even overbreathing from exercise may cause a paroxysm. In these cases, sensory impulses travel to the vagus nuclei and reflexly initiate motor (and secretory) impulses. The same may hold true in those cases presumably gastric in origin. An overdistended stomach is frequently considered a cause of attacks. Whether this leads to bronchial irritation from pressure transmitted through the diaphragm or whether afferent impulses travel up the pneumogastric nerve and then down the bronchial branches, is unknown. Nasal irritation that leads to attacks, likewise is a sensory-motor reflex.

Without doubt, by far the greatest number of cases of bronchial asthma are due to irritation of the efferent vagus endings in the bronchi. True bronchial asthma is for the most part an expression of allergy which implies a hypersensitiveness to substances foreign to the body. Asthma results under certain conditions when these enter the body either by inhalation, absorption from the gastro-intestinal tract or by parenteral injection, and access to the bronchial vagus endings must be by the blood stream. In this connection, the experiments of Auer and Lewis suggest the mechanism involved. It will be recalled that they induced bronchospasm in anaphylactic guinea-pigs even when the vagus nerves were severed and in decerebrate animals but failed to produce shock when vagus nerve endings were paralyzed by atropine.

Hence the injected antigen was carried to the vagus nerve endings by the blood.

In considering the possible reactions involved in the stimulation of efferent vagus endings, and these at best are imperfectly understood, it becomes necessary to inquire why it is that certain persons are subject to bronchial asthma, and others not.

For a long time, asthma has been recognized as an hereditary condition. Cullen (1784) and Ryan (1793) suggested this, whereas some years later Eberle[85] (1831) and Goode[86] (1836) maintained that it was a generally accepted opinion. Andral (1839) stated that a number of early writers placed heredity, which he defined as an organic disposition to contract the affection, as a prime cause of asthma. This opinion has persisted and recently has been confirmed by substantial statistics. This indicates that asthmatics may differ from normal individuals insofar as heredity is concerned. The questions then arise as to what these individuals inherit, and whether such inheritance manifests itself by constitutional changes.

Although asthma has been mentioned frequently as a gouty tendency, and from time to time has been associated with diabetes, cholemia and various skin manifestations, it was not until recent years that it became recognized as an expression of a constitutional defect. Czerny,[87] the pediatrician, was the first to recognize that certain children are liable to one or more of a group of clinical conditions, all of which are due to exudative lesions. He noted in these children, a constitutional variation from other children, which he called an "exudative diathesis;" a tendency to exudations. When this occurs in the skin, it gives rise to eczema, lichen scrofulosum and urticaria. Later angioneurotic edema and other dermatoses were included. These same children are apt to have nasal catarrh, an exudation into the nasal mucosa; asthma, an exudation into the bronchial mucous membrane; and sudden vomiting and diarrhea following the first ingestion of certain foods, as egg. This is an expression of an

exudation into the gastro-intestinal mucous membrane. The latter conditions, with certain others, later became included as expressions of an exudative diathesis. Czerny's contentions have met with general acceptance. From the standpoint of bronchial asthma they are of prime importance as they indicate that bronchial asthma is not a disease *per se*, but rather one expression of an underlying constitutional defect.

There is ample confirmation of the association of bronchial asthma with other exudative conditions, particularly nasal catarrh (vasomotor rhinitis) and hay-fever, eczema, urticaria, angioneurotic edema, and the gastro-intestinal disturbances mentioned above. This not only is a common clinical experience, but has statistical support. (Schloss,[88] Peshkin,[89] Smith[90]). This tendency to exudation in children lessens gradually as they grow older, which conforms to the fact that asthma begins usually in the earlier decades, as do eczema and hay-fever.

These exudative conditions are hereditary. Drinkwater[91] traced the occurrence of asthma through three generations of one family and found that it conformed to Mendelian law and was a dominant characteristic. Cooke and Vander Veer likewise studied hay-fever in 78 families (with 220 children) in which there was a single or double inheritance and also 148 cases (631 children) with a negative family history. Their percentages are sufficiently close to the theoretical to indicate that the tendency is inherited as a dominant characteristic. Abagail Smith[90] recorded the occurrence of asthma, hay-fever, eczema and other expressions of exudative diathesis through five generations of a single family and she, too, concluded that this condition corresponds to Mendelian law and is inherited as a dominant. Its expression in the descendants may not be the same as in the forebears. Thus, a parent with asthma may bear children who develop only hay-fever, or eczema or both without asthma, and the converse may occur also.

It becomes evident, therefore, that true bronchial asthma is often an expression of an inherited constitutional variation from normal individuals, of which a tendency to exudations is the underlying pathological process. Little is known concerning the mechanism of these exudations. They are ascribed to an increased permeability of the capillaries of the skin and mucous membranes. This argues in favor of a mucosal edema as the immediate cause of bronchial narrowing in asthma. Coincident smooth-muscle spasm occurs also, not only in asthma but in the gastro-intestinal conditions ascribed to exudative diathesis.

Some years after Czerny's investigations, bronchial asthma came to be considered an expression of anaphylaxis (to which the terms human hypersensitiveness, and allergy were applied later). It soon became evident that hay-fever, vasomotor rhinitis, eczema, and urticaria also were expressions of the same process. Thus, the very conditions that were recognized first as pathologically similar came to be studied from an entirely new angle, their immunological identity. They became associated with allergy largely through the development of the skin tests to foreign protein substances, for it was found that positive reactions occurred in individuals with bronchial asthma and its associated conditions. The skin reaction is merely a localized edema, or exudation at the site of contact of the cutaneous cells with the foreign substance applied there. It is another expression of an exudative tendency and gives visible evidence of a constitutional variation which does not occur in most individuals.

There is little to be found on physical examination of asthmatics between their attacks, and before a complicating emphysema has occurred, that would single them out as constitutionally different from other subjects. One fact has been noted by a few observers, namely, that their body configuration indicates a status thymolymphaticus far more often than occurs normally. Czerny noted the frequent association of status lymphaticus with exudative diathesis.

This is difficult to detect in adults excepting in males after the second decade. Here the condition is identified by a scantiness of facial and body hair, abundant scalp hair with a low brow line, a transverse pubic hair line of the feminine type, wide-arched thighs and a delicate smooth skin. Symmers[92] in over 5000 autopsies studied the incidence of status lymphaticus in adult males, and found it about 8 per cent. Emerson[93] noted 22 per cent in 1000 patients in alcoholic wards. A far larger occurrence of complete or partial status has been noted among asthmatics. Not much can be argued from this finding as the group of patients available (adult males) is not sufficiently representative. It does suggest a constitutional variation and again associates bronchial asthma with exudative diathesis.

In an asthmatic, then, we are given, usually, an individual with a tendency toward a particular pathological process which, in turn, is intimately associated with a hypersensitiveness to particular foreign substances. On adequate contact with these substances, asthma results. The asthmatic paroxysm, however, is dependent on vagus stimulation, and it is interesting that Eppinger and Hess considered not only bronchial asthma but other expressions of exudative diathesis also, as conditions of increased vagus irritability (vagotonia).

Just what reactions occur when specific foreign substances enter the system of an asthmatic and how they come to stimulate vagus nerve endings is unknown. There is some indication that these protein-like substances are broken down through the action of eosinophiles, which occur in large numbers in the lungs of asthmatics. This is suggested by the recent work of Oeller[94] and of Schilling.[95] These investigators found that if chicken erythrocytes, which are nucleated, be injected intravenously into normal guinea-pigs, these cells remain intact and may be identified in the blood stream for a considerable time. If, however, after several days, these animals be reinjected, a remarkable process is observed in the lung capillaries. An immediate

hemolysis of the foreign erythrocytes occurs and their freed nuclei degenerate quickly, largely through the action of the capillary endothelial cells which become phagocytic. There is a localized edema of the surrounding tissues and a widening of the lymphatics, capillary dilatation and, as Schilling pointed out, a great accumulation of eosinophilic leukocytes. These cells may then be seen to migrate through the capillary walls and to accumulate in the pericapillary and peribronchial tissues. Finally, they penetrate into the bronchi and within four hours have been found as a thick ring surrounding the bronchioles, as well as in their walls and lying free in the lumen. Here, there forms an eosinophilic exudate resembling the sputum of bronchial asthma. This process subsides gradually, and the lungs assume their normal aspect. Schlecht and Schwenker[96, 97] had shown previous to this, that in anaphylactic animals, eosinophiles accumulate at the sites of protein invasion and are found particularly in the lungs. This suggests that in conditions of hypersensitiveness in man as well as in anaphylactic animals, foreign substances entering the body are carried to the lungs which become the site of their destruction in which eosinophiles participate. The fact that the process is self-limited suggested to Schilling that this may bear a relation to the limitation of asthmatic attacks.

What becomes of foreign substances thus destroyed, and how they stimulate the vagus endings, is still a mystery. The subject is one of enormous complexity of which only a few isolated facts have been established. For instance, it is known that stimulation of the vegetative nervous system is associated with changes in the concentration of certain ions. Wollheim[98] found that sympathetic stimulation is accompanied by an increase in calcium concentration in the blood. Conversely, Zuntz and La Barre[99] showed that in anaphylactic shock, which is a vagus effect, the total blood calcium becomes markedly lowered. Also, in asthma, the blood calcium has been found to be reduced (Billigheimer[100]).

Zondek[101] pointed out that K and Na ions stimulate the vagus whereas Ca ions depress it. The existing evidence, however, is not sufficient to establish whether ionic concentrations are the cause or the effect of stimulation of the vegetative nervous system. One is tempted to believe that nerve stimulation results from ionic concentrations in the tissues, an assumption advanced by Dresel and Katz.[102]

From these indications and much similar work of physico-chemical nature which is engaging so much attention at this time, it is seen how involved these processes become. There is, apparently, an immediate relationship between electrolytic actions (some of which are controlled by secretions of ductless glands) and stimulation of the vegetative nervous system. The physico-chemical disturbances seen in anaphylactic shock[99, 103] link immunological reactions with these processes. The intricacy of these reactions give credance to the contentions that asthmatic paroxysms may be relieved by many apparently unrelated measures. Injections of colloidal suspensions, milk, peptone, vaccines, tuberculin and sulphur; roentgen-ray and ultra-violet ray therapy; fever and diathermy—all these may well disturb the balance of the process with which vagus stimulation is associated.

Only in recent years has bronchial asthma come to be looked upon as something more than an effect resulting entirely from a single process, be that infection, psychic disturbance, nasal irritation, allergy or mechanical irritation of the bronchi. A broader conception of the disease, although as yet imperfectly understood, is leading to a more exact understanding of the reactions involved and thereby offers a wider outlook for rational therapeutic measures.

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CHAPTER IV.

PATHOLOGICAL FINDINGS IN BRONCHIAL ASTHMA.

An asthmatic paroxysm is considered a functional disturbance, and, since death during an attack is exceedingly rare, there is very little material available for study. Rackemann[1] was able to collect from the literature but 11 such cases that have come to autopsy. Kountz and Alexander[2] have since added 3 more. Postmortem examinations have been reported in some 20 other patients with bronchial asthma in whom death was attributed to one of its complications or to intercurrent disease.[3, 4]

Since the immediate disturbance in bronchial asthma occurs in the bronchi, the morbid anatomy of these structures has been studied intensively in a few cases.[4, 5, 6, 7] The difficulties of interpreting pathological changes that occurred during life from anatomical sections are many. For instance, the distinction between a contracted and an hypertrophied muscle is by no means obvious, and might be revealed only by particular study such as counting the number of nuclei in a given area and comparing this to the number present in normal muscle tissue. Or again, increased epithelial folding may be due to muscle contraction, but there is no way of estimating the degree of spasm that persists after death, and experiments with anaphylactic guinea-pigs with this in view have been very unsatisfactory. Moreover, postmortem findings were not always uniform. This discrepancy is attributed to the varying duration of the disease, the effects of complications, and the fact that some patients died during an attack, and others between paroxysms. Despite such differences, however, some very suggestive information has been obtained.

MORPHOLOGICAL APPEARANCE OF THE BRONCHI AND ALVEOLI.

Reference will be made to Fig. 1 (Chapter II), a schematic representation of a medium-sized bronchus, which is taken from Hüber and Koessler's article; and changes in the separate structures indicated will be considered in order.

FIG. 3. Cross-section of a 2 mm. bronchiole from a case of fatal asthma. The lumen is dilated and contains much exudate. The epithelium is thinned and the surrounding alveoli compressed.

The epithelium of a bronchus about this size normally consists of a single layer of ciliated columnar cells attached to a basement membrane. As the bronchi become still smaller, these flatten to cuboidal shape and may or may not be ciliated, and finally in the bronchioles they become squa-

mous. Goblet cells which are numerous in the larger bronchi gradually disappear and are found only occasionally in the bronchioles. The basement membrane upon which these cells rest is a very distinct hyaline-like structure. Normally, the epithelium is thrown up into shallow longitudinal folds

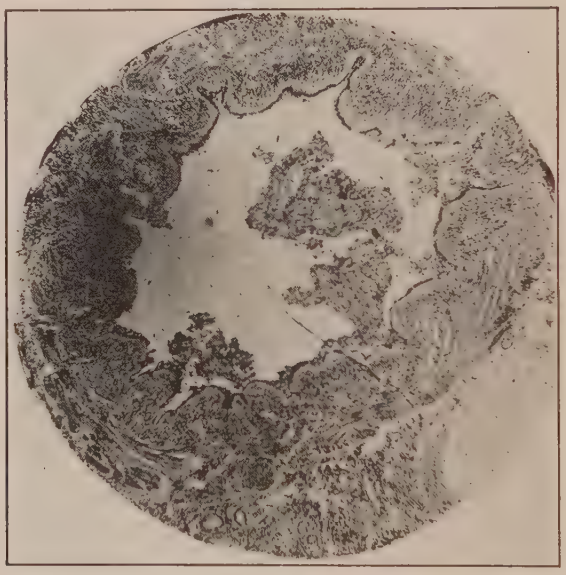

Fig. 4.—Cross-section of 5 mm. bronchus from a case of fatal asthma. The lumen is constricted and partially obstructed by exudate. The epithelium is thrown into folds.

which, according to Hüber and Koessler, at times may be quite deep.

In postmortem sections of asthmatics, the epithelial structures may show two distinct variations. The smaller bronchioles are found occasionally to be distended and thin-walled as if pressure had been exerted within them against obstruction higher up. In this condition, the epithelium is thinned and flattened out, and the surrounding alveoli appear to be compressed (Fig. 3). In the same individual,

the condition may be quite reversed as the bronchi become a little larger. Here, the air space is greatly encroached upon by the epithelium which is thrown into deep folds (Fig. 4). Identical pictures are seen in sections of the lungs of guinea-pigs that have died in anaphylactic shock. It is, therefore, a fair inference that this folding results from a bronchospasm of the surrounding smooth muscle which squeezes the epithelium into this shape. This folding varies in different places, and at times is but slight, which may be due to irregular muscle contraction, or possibly to release of post-mortem bronchospasm.

Occasionally, there is an actual hypertrophy of the epithelium and instead of a single layer of cells there may be two or more. The basement membrane also is often wider than is normally seen. One quite constant finding is the increase in the number and size of the goblet cells. This was emphasized by Fraenkel who found some to measure more than 20 μ in height.

The subepithelial tissue layer is an artificial zone designated as such by Hüber and Koessler and defined as "the area of loose connective tissue lying just beneath the epithelium in all divisions of the bronchi down to the bronchiole. It contains numerous capillaries, fine elastic fibers, small round cells and connective-tissue cells, and mingles in its outer portion with a coarser elastic fiber layer. This layer is prominent in all divisions of the bronchi down to and including the bronchioles, forming distinct longitudinal bundles of fibers which show some irregularities in the direction where the gland ducts, vessels, etc., penetrate it. In these places, the fibers may appear to form distinct circular bundles." These observers who made comparative measurements of the width of various elements in the bronchi of asthmatics and non-asthmatics found little difference in the thickness of the subepithelial layer in bronchi of less than 2 mm. outside diameter. In those larger than this, the width of the subepithelial layer progressively increased in the asthmatic

group, and in bronchi of 5 mm. it became about twice as thick as the average normal. In still larger tubes it became proportionately reduced. This thickening was produced by hyperemia and also by cellular infiltration, particularly by round cells and by eosinophiles. Kountz and Alexander confirmed these measurements in their cases excepting that they found widening to begin in still smaller bronchioles.

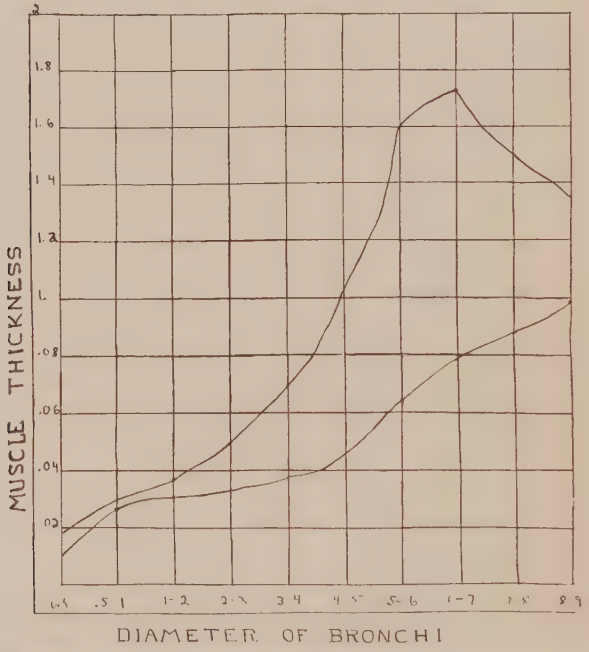

FIG. 5. Graphic representation of ratio of muscle thickness to diameter of bronchi. Upper line equals composite curve of 3 cases of bronchial asthma. Lower line equals normal controls.

The arrangement of the bronchial musculature has been described in Chapter II. Inasmuch as bronchial asthma presumably is a bronchospastic condition, any pathological changes noted in these structures become of utmost importance. Although hypertrophy had been mentioned by

Marchand[8] and Mönckeberg,[9] its occurrence was not established definitely until Hüber and Koessler's painstaking measurements were published in 1922. They averaged a large number of measurements taken from bronchi of various sizes from 6 asthmatics and compared them to those of 7 non-asthmatics. Determinations of muscle thickness were made at right angles to the tubes. A composite graph of 3 cases of Kountz and Alexander is recorded in Fig. 5. This curve conforms essentially to that of Hüber and Koessler. It will be noted that little widening occurs in the asthmatic group in bronchi of less than 2 mm., but in tubes larger than this, definite increase in muscle thickness appears until it becomes almost three times greater than the controls in bronchi 5 mm. wide. As Hüber and Koessler point out, this increase in muscle thickness may signify a true increase in the size and quantity of the muscle cells and, therefore, a true hypertrophy, or it may be due to an increased contraction of muscle. They note, however, that increased smooth-muscle contraction implies, with few exceptions, increased muscle tonus and the increased thickness of smooth muscle due to contraction is the morphological expression of hypertonus. These factors, moreover, hypertonus, repeated contraction and hypertrophy are functionally related and probably all of them are involved in the production of increased thickness of the muscle tissue in the bronchi of the asthmatic. These findings give great credence to the bronchospastic theory of asthma.

Thus far, it appears that the principal site of the asthmatic lesion lies in bronchi of about 5 mm. in width, for here the lumen is most encroached upon, and both muscle and subepithelial tissues the thickest. That obstruction occurs here is reflected in the occasional finding of greatly widened bronchioles below this, and it appears as if they became distended by the pressure of trapped air which expiratory forces tried to expel through the obstruction above. So great, apparently, may this become that an actual rupture

of the epithelium has been seen with extrusion of the subepithelial tissue into the lumen (Fig. 6).

Although muscle hypertrophy is present in all cases, evidence of mucosal edema is not so striking. Vascular engorgement plays some part in the widening of the subepithelial layer, and a marked mucosal congestion was noted by

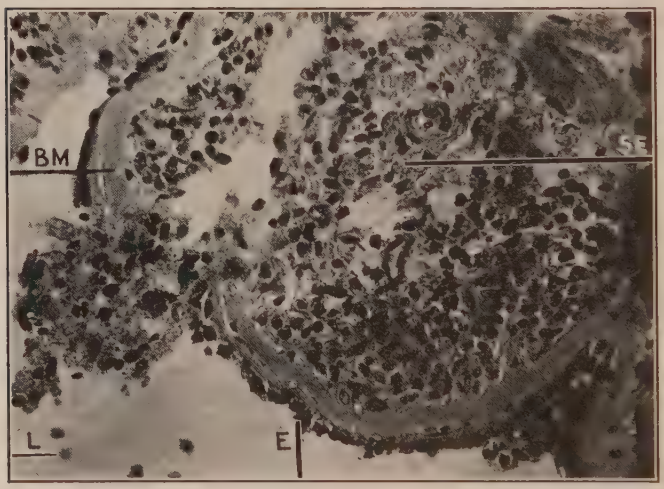

FIG. 6.—Section (high power) of bronchial mucous membrane from a case of fatal asthma. There is an actual rupture of the basement membrane and epithelium with extrusion of subepithelial substance into the bronchial lumen. *L*, equals lumen; *E*, epithelium; *BM*, basement membrane; and *SE*, subepithelium.

Fraenkel,[6] Jezierski[10] and particularly by Mönckeberg,[9] but this lesion is by no means constant.

In asthmatics, the mucous glands appear enlarged although their irregularity in shape makes it difficult to measure them. Their activity is represented by an increased amount of mucus found within them and in the bronchial lumen. Occasionally a mucoid degeneration of the secreting cells may be observed.[2]

Another occasional lesion[2] is a curious degeneration of

cartilage which is represented by vacuolization (Fig. 7). The cause of this is not understood.

The constant presence of eosinophilies will be discussed. Not only do they surround the muscle but they actually have been found invading its substance and destroying it[2] (Fig. 8).

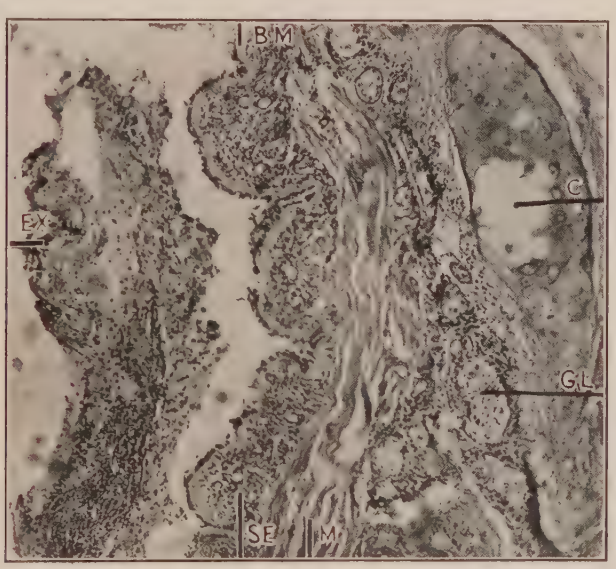

FIG. 7.—Longitudinal section of a 5 mm. bronchus from a case of fatal asthma. The following lesions are shown. *EX*, equals exudate in the bronchial lumen; *BM*, widened basement membrane; *SE*, thickened subepithelial tissue; *M*, hypertrophied bronchial muscle; *GL*, degenerated mucous gland; and *C*, vacuolar degeneration of cartilage.

In one case of fatal asthma sections from the nasal mucous membrane were studied.[2] The epithelium was markedly hyperplastic and underneath this was a prominent hyaline basement membrane. The submucous connective tissue was loose and edematous and contained accumulations of lymphocytes and eosinophiles. The glands were very prominent and in them a mucoid degeneration was present. These

findings are strikingly similar to those observed in the bronchi, and indicate an active participation of the upper respiratory tract during attacks. Clinically, this is frequently the case.

Emphysema as a consequence of asthma is shown on postmortem examination, by enlargement of some of the alveoli

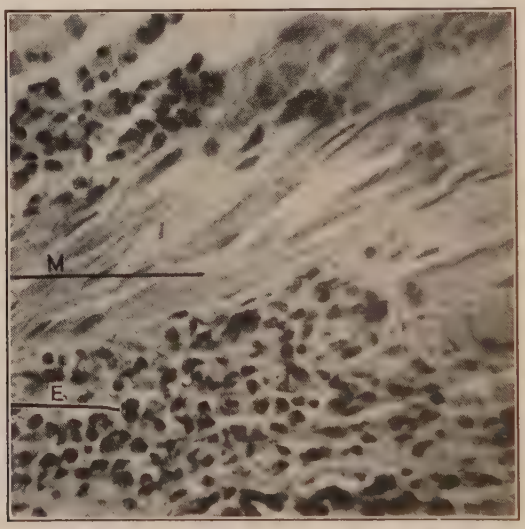

FIG. 8.—Section (high power) of bronchial muscle with invasion and destruction by eosinophiles. *M* equals muscle bundles and *E* equals masses of eosinophiles.

with thinned and occasionally ruptured interalveolar septa. In places, large emphysematous bullæ occur. A notable finding is the uneven distribution of the emphysema. The apices particularly are involved in some instances; in others, the bases. In one lung, marked emphysema, normal alveoli, and atelectasis, all were seen. This may have some bearing on the fact (which will be detailed elsewhere) that minute volumes of respired air during a paroxysm have normal values, as if there were sufficient uninvolved lung tissue to compensate for the affected portions.

Hüber and Koessler were the first to point out the occurrence of absorption atelectasis in bronchial asthma. Occasionally, an area of atelectatic lung tissue surrounds occluded bronchi and it is assumed that when air no longer can enter these alveoli, their contained gases are absorbed into the surrounding circulation, with a consequent collapse of the air spaces.

The observations of Sonne[11] that pathological sections of emphysematous lungs show the bronchi apparently to be pulled upon and thus widened, have not been confirmed. Clinical significance has been given to Sonne's contention in that it may explain a diminution in the severity of paroxysms occasionally seen when marked emphysema has occurred.

As a consequence of emphysema, secondary changes occur. These include the characteristic thoracic deformity, low position of the diaphragm and occasional hepatosis, the elongation of the vertical diameter of the heart and possibly myocardial changes in some cases.

THE HEART.

No reference was found dealing with the morbid anatomy of the heart in bronchial asthma. There long has been a widespread clinical assumption that as the disease progresses, the right ventricle hypertrophies and dilates because of circulatory obstruction met with in emphysematous lungs. Clinical observations which tend to refute this inference will be considered (Chapter VI) but critical evidence must rest on postmortem findings. There are but 15 cases in which sufficient data are available to form a reasonable conception of the state of the heart. Of these, 5 were complicated by superimposed diseases: nephritis, rheumatic fever, etc., which obscured the issue as to whether cardiac lesions were caused by asthma. Of the remaining 10 cases, right ventricular hypertrophy occurred in 2. In 1 of these, it could be ascribed to no cause other than bronchial asthma. In the

other, both ventricles were thickened which throws some doubt upon the incrimination of asthmatic paroxysms, for there is no reasonable assumption of a mechanism in this condition which should enlarge the left ventricular wall without pathological changes other than hypertrophy, and none were found. Consequently, it is possible that the right-sided hypertrophy was a consequence of an initial left-sided enlargement of undetermined cause. There were 2 instances of right ventricular dilatation and in the remaining 6 cases no pathological changes were noted. From this review, no conclusions can be drawn, but it is noteworthy that in 2 cases which were observed for a long time during life and in which peripheral signs of apparent cardiac failure were observed, the hearts were normal.[2] These clinical signs, therefore, may have to be reinterpreted (Chapter VI).

SPUTUM.

Some of the pathological processes which occur in the bronchi of asthmatics are reflected in the sputum. It thereby possesses characteristics which are so distinct that their recognition virtually establishes the diagnosis of the disease. Mucus is abundant and appears as homogeneous gelatinous masses for the most part. However, where apparently it has been pressed within the constricted bronchi, it presents a typical morphological appearance. Grossly, this is seen as a grayish-white or yellow mass a few millimeters in diameter. When shaken in physiological salt solution, it unravels into a fine spiral which is usually somewhat less than a millimeter in width and from 1 to 2 cm. long. These masses were noted in asthmatic sputum by Laennec who called them "perles." The configuration of the spirals was described by von Leyden during his study of crystals in asthmatic sputum, but Curshmann[12] with whose name they are identified, elaborated upon their microscopic appearance. There is a central core of mucus which is either a spiral with wide curves or almost

straight, about which are wound threads of mucus in close spiral formation. There are many varieties of this arrangement both in size and morphology. Curshmann believed that these particles were casts of small bronchioles made by compression of mucus within their lumina. This is quite possible since Fraenkel recorded the presence of spirals in pathological sections of bronchioles from a fatal case of asthma, although in tubes as small as this, mucous glands are rare.

Why mucus should assume a spiral arrangement is open to question. It may be that the lungs which are thought to open and close in a fan-like movement during respiration may twist the bronchi during forced expiration and, in all probability, this occurs. Hoffmann[13] demonstrated that the tough mucus in asthmatic sputum could be moulded by adequate pressure and manipulation into spiral formation and Gerlach[14] produced the same effect by arranging mucus threads in a glass tube and then blowing air in and out. The importance of spirals in asthmatic sputum lies in the fact that they are found, with but rare exception, in no other condition. A feature which identifies them with asthma is the presence of eosinophiles which are frequently adherent to them. They sometimes contain round cells also and obviously both of these types of cell become attached to the mucus either in the bronchial wall or in the lumen.

Leyden[15] in 1872 identified crystals in the sputum of asthmatics and he believed that, conceivably, they could induce attacks by their irritation of the bronchial mucosa. He described these as found within small round masses about the size of a millet seed and of tough consistency. When these were pressed between cover-glasses they appeared as crumbling, dry, smooth material. In the center of the mass were colorless, needle-like crystals, varying widely in size but consistent in shape. It is apparent that the masses within which Leyden found crystals, were perles. Similar crystals had been described first by Rollin and Charcot in a spleen

from a leukemic patient, and later in a variety of conditions by other observers, such as in the sputum from cases of bronchial catarrh and fibrinous bronchitis; in the blood of a patient with leukemia; in pregnancy; and in mucus from the common bile duct.

Leyden studied some of the chemical properties of these crystals. They are soluble in warm water, mineral acids and most organic acids and alkalies, and are insoluble in cold water, ether, alcohol and chloroform. Charcot-Leyden crystals are shaped like hexagonal pyramids resembling tyrosin crystals. For a long time an identity to spermine crystals (Böttcher crystals) has been claimed and recently this has been shown to be highly probable.[16] Charcot-Leyden crystals are by no means constant in asthmatic sputum and are found most often after the sputum has stood for some time. This suggests that they may not occur as crystals within the bronchi.

Petry[17] was the first to suggest that Charcot-Leyden crystals are formed from eosinophiles and this theory has recently received considerable attention, particularly from the work of Liebreich[18] and of Neumann.[19] Liebreich mixed normal whole blood immediately after withdrawal with an acacia-citrate preparation and centrifuged the mixture according to a particular formula. After a certain time he found a large number of eosinophiles, and Charcot-Leyden crystals appeared also. Liebreich sought to prove that it was the eosinophile granules from which the crystals were formed. Storm van Leeuwen and Nijk[20] offered the suggestion that the acacia-citrate mixture may have contained sufficient calcium to have formed calcium phosphate crystals. They believe that Charcot-Leyden crystals are an unstable crystalline form of calcium phosphate. Neumann modified Liebreich's technique and believed he could demonstrate that a substance which is derived from eosinophiles, is produced during a particular phase of coagulation, and that this is responsible for the formation of Charcot-Leyden crystals.

His technique demands an exactitude which is difficult to repeat. These experiments of Liebreich and of Neumann, which are numerous, are suggestive but more substantial evidence is required before it can be accepted as a fact that Charcot-Leyden crystals depend upon eosinophile cells for their formation.

EOSINOPHILES.

The rôle of eosinophiles in bronchial asthma is unknown. It has been recognized for a long time that an eosinophilia is produced in certain animals on reinjection of a foreign protein substance. Schlecht[21] was the first to point this out. In 1912 he and Schwenker established definitely that a local eosinophilic accumulation could be induced in previously sensitized guinea-pigs by reinjection of the specific protein. They introduced various protein-containing substances such as serum, egg albumen, and fibrin into the peritoneal cavity and noted little eosinophilic response until after the second injection which was made at the end of the antianaphylactic period. A marked local accumulation of eosinophiles developed. These observers worked also with protein derivatives and found that peptone induced less response and amino-acids, none at all. They found, moreover, that the lungs of guinea-pigs subjected to mild anaphylactic shock contained large numbers of eosinophiles. Likewise, as has been noted, Oeller, and Schilling have observed the mobilization of eosinophile cells in the lungs on reinjection of foreign erythrocytes. Koessler[22] has noted that a blood eosinophilia is constant during attacks of hay-fever and that, as a rule, no increase of these cells appears in the blood in the months when these patients are free from symptoms. Eyermann[23] has found an eosinophilia in the nasal secretions of patients with allergic coryza. Eosinophiles, then, appear to be called forth by foreign proteins entering the body and to be attracted to the sites of such protein invasion. Apparently they are concerned with proteolytic digestion but their exact function is not

understood. One obstacle to the study of this problem lies in the failure thus far, of devising a method wherein these cells may be isolated and their proteolytic properties studied *in vitro.*

For a long time it has been disputed whether eosinophiles come from the bone-marrow alone or whether they may be formed locally in the tissues. Although Ehrlich believed that the bone-marrow was responsible for their production, Stschastruji[24] noted their formation *in situ* after the intraperitoneal injection into guinea-pigs of a foreign-protein substance (red blood cells). The neutrophiles attracted there were observed to assume eosinophilic granulations. There has been considerable substantiation of each contention. Hüber and Koessler considered this problem carefully insofar as the bronchial mucosa in asthma is concerned. They state that the contention of autochthonous local eosinophilia is based mainly on the occurrence of mononuclear cells in the sputum and bronchial tissue, the complete absence of such unicellular elements in the circulating blood, and the enormous number of eosinophile cells found in the tissues, far too many to have accumulated from the blood even if it showed a considerable eosinophilia. They refute the first asertion after a careful examination of the cells with an apparent mononuclear structure, as they found that viewed from various planes, most of these were in reality polymorphonuclear cells. Those which did appear to be mononuclear were considered degeneration forms of polymorphonuclear eosinophile cells whose nuclear substance had undergone regressive metamorphosis. These observers answer, also, the argument that the tissue accumulation exceeds the number of eosinophiles that could be transported by the blood. They made an arithmetical calculation based on the estimation of Heinke and Deutchmann[25] that during an asthmatic attack the eosinophilies in the circulating blood decrease about 80 per cent. This, in terms of several liters of blood, would make possible an enormous accumulation of these cells in the tissues.

In bronchial asthma, the presence of eosinophiles in the sputum is of utmost diagnostic importance as no disease, other than rare parasitic invasions of the lungs, has a pronounced sputum eosinophilia.

Other than an eosinophilia, there is nothing notable in the blood picture of bronchial asthmatics unless a secondary bronchitis supervenes. Then, a neutrophilic leukocytosis may occur.

Francis[26] made hematocrit readings during asthmatic attacks but found no increase in the red blood-cell volume.

FUNCTIONAL PATHOLOGY.

There is very little available data concerning respiratory function during asthmatic attacks. Staehelin and Schütze[27] measured minute volumes in 4 patients and found a marked increase during paroxysms. Their results which are quite striking, are tabulated as follows:

Case.	During attacks, liters.	Between attacks, liters.	Normal controls, liters.
I	15.0 to 16	10 to 11.0	
II	17.4 to 18	12 to 12.5	7.2
III	12.0 to 13		
IV (a very small woman)	8.4		

This over-ventilation was accomplished by increased depth of breathing rather than by an increase in rate. These authors noted also that the prolongation of expiration as compared with inspiration when recorded by a pneumograph, was but slight despite a prevailing opinion to the contrary.

These findings of Staehelin and Schütze require confirmation especially as they conclude that over-ventilation in asthma is not conducive to a CO_2 accumulation in the blood. The cyanosis, which probably is not cardiac in origin, often observed during a paroxysm tends to refute their work. In this connection, Meakins and Davies[28] noted that during severe paroxysms the oxygen saturation of the arterial blood may be much below normal, with a coincident increase of

carbon dioxide. In milder cases they found that although the saturation of the arterial blood was somewhat reduced, this was not pronounced. Examination of the lungs in these cases indicated that obstruction to the bronchi was not uniformly distributed and that there were considerable areas functioning properly. These uninvolved areas tend to compensate for the affected ones, and through them the accumulated carbon dioxide in the blood is discharged. Meakins studied the urinary acidity in cases of varied severity and found that after severe paroxysms with marked carbon dioxide accumulation in the blood, the urine was highly acid. On the other hand, in those cases where presumably only portions of the bronchioles were affected and where there were uninvolved areas of lung to get rid of the accumulated acid, the urinary acidity was much reduced.

Kuhlmann[29] measured the reduction of alkalinity of the blood by estimating the carbon dioxide combining power in one case of long-standing bronchial asthma immediately after an attack and found a reduction to 36 per cent in contrast to his normal averages of 57 per cent. Billigheimer[30] has reported a reduced blood calcium in bronchial asthmatics.

Excepting the observations of Stäuble that the viscosity of the blood is increased, no estimations of the physical properties of the blood during asthma were obtained.

The immunological reactions of asthmatics are described in Chapter V.

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CHAPTER V.

THE IMMUNOLOGICAL ASPECTS OF BRONCHIAL ASTHMA.

Until quite recently, the nature of bronchial asthma had been studied by pshysiological methods almost entirely. There seemed to be no thought of an immunological factor until the year 1910 when, as has been stated, Meltzer called attention to the similarities between the lungs of asthmatics and those of guinea-pigs dead from anaphylactic shock. The subject of anaphylaxis at that time was receiving an increasing amount of attention, but as yet it had remained a laboratory problem with little clinical application. During the succeeding five years the researches of Cooke,[1] Goodale,[2] Walker,[3] and others, established the existence of immunological factors underlying bronchial asthma which simulated many of those underlying anaphylaxis. Since then the entire complexion of the literature dealing with asthma has changed and the study of the disease from a physiological standpoint has become superceded almost entirely by immunological research. The latter, which is still developing, has revealed new facts so rapidly that revisions of theories and terminologies have made a concise appreciation of the subject most difficult.

DISTINCTION BETWEEN ANAPHYLAXIS AND ALLERGY.

The distinction between anaphylaxis and the mechanism which underlies bronchial asthma, is an important one. The two processes were considered one until gradually it became evident that the so-called anaphylaxis in man violated many of the principles laid down as criteria for anaphylaxis. Then other terms such as "protein sensitization," "human

hypersensitiveness," "atopy" and "allergy" were suggested to denote the process in humans as distinguished from that in the laboratory animal. The word "allergy" is now most widely employed, although there is considerable objection to its usage as it is an adaptation and therefore is confusing.

Without discussing many controversial points, the essential differences between anaphylaxis and allergy, insofar as asthma is concerned, will be set forth.

"Anaphylaxis" is a term coined by Portier and Richet[4] to denote a state of sensitivity which is manifested on the reinjection of antigenic substances into an animal under given conditions. Until the publication of their experiences, injection of an antigen was found usually to protect an animal against subsequent injections, and an animal thus was made prophylactic to them rather than sensitive or anaphylactic.

Anaphylactic shock is manifested by a definite train of symptoms which varies according to the species of animal used. Thus, in the three animals most studied, the guinea-pig, the dog and the rabbit, the lesions producing shock are quite different, although they are always the same for a given species, no matter what antigen be used to induce it. Thus, in guinea-pigs, spasm of the bronchi, in dogs circulatory changes, and in rabbits lesions in the pulmonary vasculature are the essential findings.

In man, the prototype of anaphylaxis, namely allergy, is manifested by lesions which are confined largely to the skin and to the respiratory and gastro-intestinal tracts. These establish clinical conditions such as bronchial asthma, hay-fever, vasomotor rhinitis, eczema, urticaria with angio-neurotic edema and certain gastro-intestinal disturbances. Each of these may occur alone, or two or more may be present simultaneously. The processes underlying all of these conditions are edema, or smooth-muscle spasm, or both. This group of anatomical lesions is distinctive for man, although as has been stated, some of them are simulated in the guinea-pig.

Anaphylactic shock can be induced only by soluble protein

substances, and with few exceptions, almost all such proteins are capable of producing it. In the development of the earlier conceptions of allergy, it was believed that this was true also for man, and hence the term "protein sensitization" to denote this phenomonon in humans came into general use. It was soon realized, however, that certain non-protein substances, particularly drugs such as aspirin could induce severe allergic manifestations. Recently, efforts have been made to analyze various allergens[5,6,7] such as ragweed pollen and horse dander, and to determine from such complex structures the nature of the fraction which induces allergic reactions. Coca and Grove have found that the allergenic portion of ragweed pollen gives no protein reaction at all, and its nature is unknown, but that of horse dander, on the other hand, retains characteristics of protein. Thus, there appears to be an appreciable difference between anaphylactogens and allergens in that the former, insofar as has been determined, are proteins whereas the latter may be non-protein in nature.

Anaphylaxis is an acquired condition. The exception to this is the transmission of anaphylaxis from sensitive mothers to their young through placental tissues or milk. Under these circumstances, the offspring may be shocked by a single injection of the protein solution to which the mother had been sensitized. This inherited state, however, is of but short duration at best. In the great majority of instances, in order to provoke anaphylactic shock, it first becomes necessary to inject a susceptible species of animal with a soluble protein in order to render it sensitive. This is most successfully done by parenteral administration, although intestinal introduction under certain circumstances has been described.[8] It is noteworthy that this first injection, or sensitizing dose, gives no appreciable symptoms. It then becomes necessary to allow a period of some ten days or more to elapse during which sensitivity develops, before the second dose of the same protein which then causes shock, is administered.

In man a quite different series of events occurs. To begin with, although all susceptible species of animals may be rendered anaphylactic quite consistently under proper conditions, only a very small percentage of humans are allergic. This is accounted for by the fact that allergy is an inherited tendency, which is discussed in Chapter III. This is perhaps the most important distinction between allergy and anaphylaxis. It is a matter of dispute and some speculation as to the nature of this inheritance, for some individuals manifest allergic symptoms in infancy whereas in others they first appear only after several decades. To account for this, there are two distinct possibilities. One is that a hypersensitiveness to one or more allergenic substances is present at birth but remains subliminal, and then appears under circumstances not as yet understood. Another theory implies that there is transmitted merely a tendency to develop hypersensitiveness which manifests itself after sufficient contact with one or more particular allergens. There is some support for the latter contention, as exemplified by occupational asthmas wherein hypersensitiveness to certain allergens develop only after a considerable contact with them. Ipecac, delphinium, glue and karoid gradually cause asthma in some individuals who constantly handle them. Likewise, bakers may become hypersensitive to flour, coachmen to horse dander, and fur dyers to paraphenalenamine. Rackemann[9] has reported several such cases. Another example is seen when allergic children are placed on diets which they tolerate for a time and then often develop hypersensitiveness to some of these supposedly harmless foods. In order to substantiate the theory that one must have repeated contact with an allergen before symptoms develop, it becomes necessary to explain why it is that infants occasionally develop violent symptoms such as vomiting, urticaria, and asthma immediately after eating certain foods such as egg, for the first time. Here, previous contact conceivably may have been through transmission by the mother's

milk, although, according to Stuart[10] this is not probable. More difficult of explanation, is the discovery that individuals may be sensitive to remote substances such as pollens of foreign plants to which positive skin reactions are obtained, when no possible contact can be accounted for.

A fundamental difference, then, between anaphylaxis and allergy is that in the former condition one must deliberately render a normal animal sensitive, whereas in man, sensitivity is an inherited tendency which affects comparatively few people. Symptoms of allergy develop on adequate contact with particular substances foreign to the body. The factors which determine these symptoms are puzzling. An allergic individual, for instance, on a given diet of various foods may manifest a hypersensitiveness to but one of these, such as strawberries or shell fish, and not to others taken in greater abundance. Or again, one may come in contact with pollens year after year and develop hay-fever comparatively late in life.

A somewhat indirect indication that allergy is selective is the fact noted by Coca[6] that among more than 50 pollen collectors who came in daily contact with relatively enormous quantities of fresh pollens during several seasons, not a single case of hay-fever was observed. Ancona,[12] on the other hand, noted that in a particular region, all persons who handled the dust of a certain grain spoiled by parasitic infestation, sooner or later developed a skin eruption and frequently asthma. This phenomenon, however, was studied subsequently by Grove[13] who found that the skin reaction resembled that of dermatitis venenata (from poison ivy) and could be induced by merely handling the infected material. Intradermal tests and other immunological studies demonstrated that the phenomenon observed was not allergic in nature. Grove places the associated asthma in a special category since she found it unrelated to allergy or other recognized forms.

Anaphylaxis is identified with certain immune bodies,

particularly precipitins and anaphylactins. These play no part in the process of allergy. On the other hand, an immune body which occurs apparently in man alone and is not found in laboratory animals has recently been identified in the blood of some hypersensitive individuals. This was described in 1921 by Prausnitz and Küstner[14] and has been confirmed by De Besche[15] and studied intensively by Coca[16] and his associates who named it "atopic reagin." It is found in the serum of many allergic individuals who give positive skin tests and appears to be concerned in the production of skin reactions. The presence of "atopic reagins" in the blood may be demonstrated as follows: A drop of serum from an allergic patient giving a positive skin reaction to some allergen such as ragweed pollen, is injected into the skin of a non-allergic individual. Two hours or more later, a drop of ragweed pollen extract is injected at the same site, and a typically positive skin reaction will occur here but at no other place. This indicates that the serum from the allergic patient had the property of rendering sensitive the cells of normal skin. This passive transfer is the only way in which atopic reagins can be demonstrated. They may explain the phenomenon noted by Ramirez[17] wherein a non-allergic individual having received a blood transfusion from a donor who was hypersensitive to horse dander, soon developed asthma on contact with horses and was then found to give a positive skin reaction to this allergen.

Walker[18] has described other antibodies in the blood of individuals by means of complement-fixation and also by precipitin tests, but found that these apparently play no essential part in the mechanism of allergic reactions.

It has been shown repeatedly that the process of anaphylaxis is a tissue reaction. This is clearly demonstrated by the Dale reaction as follows: A young female guinea-pig that has been injected with some protein substance such a egg albumen is killed some two weeks thereafter. The uterus then is perfused until free from blood and one of the

horns suspended in a bath of warm oxygenated Tyrode's solution. On addition of egg albumen to the bath, the smooth-muscle strip responds by contracting. Thus, in the absence of blood elements a reaction occurs between egg albumen (antigen) and some receptive substance (antibody) residing in the muscle cells. The nature of this antibody is not clearly understood but it is frequently identified with precipitins.

In allergy, the site of reaction also is essentially in tissue cells, as demonstrated by the skin reaction. It is a matter of considerable importance, however, and one not sufficiently emphasized, that in allergy only certain cells of the body appear to participate, and these are confined particularly to the skin and to the respiratory and gastro-intestinal tracts, although the arteries and perhaps the bladder and other organs under vagus control may be involved occasionally. Not all of these participate at one time, excepting in very severe reactions. The factors that determine the site of reaction depend on various circumstances which are imperfectly understood. The portal through which allergens gain access to the body is often a dominant factor. For instance, hay-fever and vasomotor rhinitis are due almost always to inhaled antigens whereas eczema and urticaria are usually caused by foods. Asthma may be induced by either. The age of the patient appears to determine to some extent the portal of entry. In adults, inhalants are most often responsible for symptoms whereas in very young children foods are usually the offending allergens. In the latter event, food derivatives gain access to the blood stream *via* the bowel wall. They then circulate to all organs but may find the cells of the bronchioles alone receptive and asthma only, will ensue. In another individual, these same allergens may find receptive cells in the skin and eczema may appear whereas the bronchi may remain unresponsive. Or, again, in hay-fever, where the lesion is in the upper respiratory tract, only occasionally do cells lower in the tract respond also and induce asthma but in these cases, the epidermis is usually sen-

sitive and positive skin reactions are the rule. In many cases of asthma, due to inhalants, such as feathers, the skin may not be receptive and no skin reaction will be demonstrated. The same may be true in food allergy. The ingestion of milk or wheat may cause urticaria and although in such instance the deeper cells in the skin are thus responsive, the superficial cells often are not, and therefore, no positive skin reaction will appear on testing. This point will be discussed further, in relation to the skin reaction. It may well be that the cells of various organs that manifest allergy only occasionally, may be responsive if sufficiently stimulated, for when general reactions occur from an overdose of an allergen injected parenterally, asthma, vasomotor rhinitis, urticaria, angioneurotic edema and gastro-intestinal colic all may appear simultaneously, whereas the previous expression of allergy in this individual may have been but one of these.

ALLERGENS.

The foreign substances or allergens which cause symptoms are numerous and are derived from various biological sources as well as from non-biological drugs. Various classifications of allergens have been suggested depending on their derivation or upon their natural mode of entrance into the body. Although all classifications suffer from inexactness, the latter scheme is the simpler and thus there are but three groups, the inhalants, the ingestants and the bacteria.

The inhalants include animal emanations, pollens, and miscellaneous dusts. Animal matter consists of epidermal scales. Those from horses, fowl, cats and dogs are the common offenders. However, rabbits and goats whose hairs have commercial uses; cattle, sheep and other animals with which man comes in contact, all may shed their epidermal cells and thus cause symptoms. The pollens fall into seasonal groups. The trees pollinate first, then the grasses and finally the weeds. Timothy pollen represents the most common

grass, although orchard grass, sweet vernal and June grass are among those which often cause reactions. In this country, ragweed which is wide-spread, is the most common offender of the weeds. Certain plants that cause symptoms may be confined to relatively small areas. It is of interest to note that essentially all pollens that induce symptoms to any degree are wind-borne, and hence the popular incrimination of roses and golden rod as causes of hay-fever or asthma is a fallacy, as the pollen from these flowers are insect borne and rarely cause trouble. Among the miscellaneous dusts, orris root, the chief ingredient of many face powders, is one of the most frequent causes of symptoms. Others are pyrethrum, the basis of insect powders, and those allergens causing occupational asthmas such as flour, ipecac, paraphenylenamin and boxwood.

Among the foods, those most responsible for symptoms are the foods most commonly taken: wheat, milk, and eggs. On the other hand, strawberries and shellfish cause allergic symptoms frequently, as is commonly known, and a hypersensitiveness apparently may exist to any protein-containing food. It becomes a speculative matter to consider the particular digestive fraction of a food that causes symptoms and in what form it becomes absorbed through the gastrointestinal tract. Apparently, there is a high degree of specificity to such allergens. An individual sensitive to egg is usually not demonstrably so to chicken meat or to chicken feathers; also, beef and milk sensitivity do not frequently appear together. The same holds true with the inhalants, for Walker[19] has shown that but a small proportion of skins reacting to horse dander will react to horse serum also. Wodehouse[20] isolated various protein fractions of horse dander, dog hair and cat hair, such as meta-proteins, peptone, keratin, etc., and on doing skin tests with these, found great variations of reaction in the same skin. He found also that individuals react differently from one another. This observation holds true, likewise, for the casein and lactalbumin of

milk, and for the albumen, globulen, and ovomucin of egg. Presumably, the allergenic fraction gains access to the blood stream through a permeable bowel wall, although little is known of its modification through the digestive process. These allergens are quite thermostable and are effective after the usual processes of cooking, but high degrees of heat apparently destroy them as is seen in the ability of children sensitive to milk to take powdered milk which has been prepared by spraying on very hot drums.

Certain drugs occasionally cause symptoms of allergy, and these may be most violent. It becomes necessary to distinguish exaggerated normal actions and side actions of a given drug from allergic action which is confined to a given group of symptoms, no matter what the drug may be. By and large, the reactions to drugs seem to depend on the chemical molecule as a whole, insofar as the ingested substance is concerned. Thus, cases reacting to acetylsalicylic acid were found to give no reaction to salicylic acid, benzoic acid, antipyrin, sodium acetate or methyl salicylate. Occasionally, however, fractions of the molecule may cause symptoms as it has been found that iodoform hypersensitiveness is due to the CH_3 group and not to iodine or iodide. The number of drugs that have been known to induce allergic symptoms is quite considerable. Reactions may occur after ingestion or inhalation.

BACTERIAL ALLERGY.

Bacterial allergy is not, as yet, well understood, but it is engaging the attention of immunologists at the present time. One notable feature of this study is the demonstration of bacterial anaphylaxis which recently has been accomplished particularly by Zinsser and Parker[21] and by Sherwood and Stoland.[22] This indicates definitely that animals may be made sensitive to bacterial extracts.

Very early in the development of allergy, Walker[23] showed

that many individuals with symptoms of asthma gave positive skin reactions to various bacterial emulsions. Walker believed that this indicated that these patients had become hypersensitive to organisms which they harbored within their bronchi. Cooke,[24] however, found no correlation between the skin reactions to bacteria and cultures from the bronchial secretions of the same individual. He studied a series of cases.

The subject of bacterial allergy was examined further by Rackemann.[25] He isolated various bacteria from the sputum of a given patient with bronchial asthma, and then did skin tests with separate vaccines made from each of these cultures. At first this was done intradermally but this method was found to be not sufficiently specific. The technique was then changed and each vaccine was given subcutaneously and the sites examined twenty-four hours later for redness and swelling. The vaccines giving such reactions were used therapeutically, but with indifferent success. Thomas, Famulener, and Touart,[26] likewise studied the rôle of infection in bronchial asthma. They did not confine their examinations to the bronchial secretion but sought for foci also in the nose and accessory sinuses, the tonsils and intestinal tract. Materials from apparent lesions at these sites were cultured and vaccines prepared from each. Skin tests were done by the intradermal method, and two types of reactions were noted; an early one similar in time of appearance and in character to those induced by non-bacterial allergens, and a late reaction appearing twelve hours or longer, characterized by signs of inflammation. Here, again, the significance of these reactions was inferred by the therapeutic use of vaccines which gave great relief in most instances. Such reasoning is open to the criticism that non-specific vaccines and other substances such as tuberculin and sulphur also may give symptomatic relief. Moreover, the type of reaction usually encountered resembled the Schick test more than that seen in allergic hypersensitiveness.

Koessler[27] obtained bacteria from bronchial secretions and treated them by chemical methods. He was able to isolate from them certain amines which have the power to cause isolated smooth muscle to contract. This is of considerable importance as it indicates a possible source of bronchospasm in asthma. More recently, Mackenzie[28] has studied bacterial allergy in relation to infectious disease, particularly rheumatic fever. Similar studies are being carried out in relation to scarlet fever and other infections but this phase of the subject is somewhat apart from the type of allergy manifested by asthma. At the present time, it is generally recognized that bronchial asthma may be caused by infectious agents although the mechanism of this process is not as yet apparent. The great interest in this subject at the present time may soon throw more light upon it. The clinical features of these cases are discussed in a later chapter.

SKIN REACTIONS.

The development of the skin tests for the detection of the particular allergen to which an individual is hypersensitive has been largely responsible for the clinical prominence which the subject of allergy has enjoyed during the past decade. This type of skin test was recorded first by Blackley[29] in 1868 in his remarkable studies on hay-fever. In 1912 Smith[30] reported a similar skin reaction in a subject sensitive to buckwheat. Noon,[31] Cooke, Goodale, Walker, and Schloss[32] were those most concerned in the development of this test in clinical allergy. Walker employed the cutaneous or scratch method, wherein powdered allergens were placed upon a superficial scratch and dissolved there in an alkaline solvent. The preparation of these materials was worked out largely by Wodehouse. Soon after the development of the scratch method, intradermal testing, wherein an extract of the allergen is injected into the superficial layers of the skin, became widely used. Each of these pro-

cedures has certain advantages over the other which will be described in another chapter, but of the two, the intradermal method is the far more sensitive.

The ophthalmic reaction is often employed and is useful in allergy of the upper respiratory tract when skin tests are negative. In this way, direct application of the allergen is made to the conjunctiva. Obviously, this test has limitations both as to the number of allergens used and because of its temporary disfigurement.

Although the skin test still is the most important adjunct for the detection of the particular allergen to which an individual may be sensitive, its widespread adoption has brought it into some disrepute through a lack of appreciation of its significance. The failure to elicit a positive skin reaction may be due to several factors. As has been stated, an individual may have, for instance, hypersensitive bronchi, or other localized allergy, without skin involvement. Consequently, the incidence of positive reactions depends largely upon the incidence of reactive skins, which probably is not much over 50 per cent. This very important feature of allergy is not sufficiently appreciated. It accounts for many failures in skin testing. Obviously, unless the cells of the skin be sufficiently sensitive, no reaction can occur. The potency and amount of the material used, the site of application, and the method employed, all have an influence on the development of reactions and will be discussed elsewhere. Also, it is a common experience to find variations in the appearance and size of reactions at various times, whether or not the patient has received specific treatment. A reaction read as markedly positive, may be less so at another time or even, occasionally disappear. The cause of this variability in the reactive property of the skin is not understood.

Not only does an absence of skin reactions in hypersensitive individuals lead to disappointment, but positive reactions may be difficult to interpret. Depending on the method

used for testing, various degrees of reaction will be found, and the standardization of these becomes purely arbitrary. Thus, with the scratch method an erythema without wheal formation is considered a reaction by some but not by others. Or, again, in the intradermal method, the development of pseudopod shapes may or may not be deemed essential for a positive response. An occasional difficulty in the interpretation of reactions is the dermatographic skin wherein reactions are simulated by the mere mechanical application of the test. Most individuals who give skin response are multisensitive and the appearance of more than one reaction may obscure the allergen particularly responsible for symptoms. An appreciation of these difficulties leads to the necessity for certain criteria for the interpretation of significantly positive reactions. These are a history of recent contact with the particular allergen causing response, or the deliberate production of symptoms on such contact. Under such conditions the skin test becomes of utmost value.

Positive skin reactions to allergens which apparently are not responsible for symptoms may occur. This seems to indicate either that there is not adequate contact with these substances to cause symptoms, or that the superficial layers of the skin contain the only receptive cells and something more may be required to produce lesions. Eczema is the particular allergic manifestation referable to these cells but as is pointed out by Engman[33] certain mechanical factors are also essential for the development of eczema and, consequently, sensitivity here may not necessarily give rise to symptoms.

No reference to a histological study of a resected positive skin reaction has been found, although the lesion simulates an urticarial wheal. By analogy with other allergic lesions, a sudden edema takes place.

There is some dispute as to the exhaustibility of the reactive properties of the cells of the skin. Mackenzie[34] found that by injecting an allergenic extract repeatedly into the

skin of a hypersensitive subject at the same site, the positive reaction could finally be abolished, due to a local exhaustion of the reacting substances in the skin. Cooke,[35] on the other hand, repeated the same procedure and could not confirm Mackenzie's conclusion.

Although, as has been stated, there is apparently a high degree of specificity in response to allergens, it is interesting that reactions can be obtained in all human skins by histamin and according to Storm van Leeuwen,[36] by human dandruff Grant and Lewis[37] have shown that histamin probably is responsible for the wheal obtained in dermatographism. This substance has long been suspected as the cause of certain anaphylactic symptoms. It is thus a mere conjecture whether histamin or a histamin-like substance may be involved in the response of the cells of the skin on contact with specific allergens.

DESENSITIZATION.

In hypersensitive individuals much may be accomplished clinically in certain cases by the process of desensitization. Here, the process in man differs from anaphylaxis. A guinea-pig, for instance, that is sensitized and then reinjected with a dose of antigen so adjusted that it will suffer severe symptoms but survive will not be shocked again on subsequent injections of antigen. Apparently it has been desensitized completely. This does not hold true in allergy. Walker and also Alexander[38] have reported the temporary disappearance of skin reactions immediately following a severe asthmatic attack. This, however, is by no means constant. It is generally recognized (Coca[39]), that man can be but partially desensitized at best. The theory of desensitization implies that by introducing small amounts of a specific allergen into the body, it is taken up by the circulation and distributed to sensitive cells. By beginning the process with doses too small to produce symptoms, a theoretical amount of reacting bodies in the cells are used up. Thus, increasing

amounts may be injected until large doses are tolerated. Although this is doubtless an antigen-antibody response, it does not follow the laws of multiple proportion as occurs in anaphylaxis. Moreover, skin reactions do not consistently decrease as desensitization progresses. An excellent discussion of this process has been offered by Longcope.[40]

Clinically, desensitization is particularly successful with certain allergens, notably pollens, horse dander, orris root, and some other dusts. The same thing may be accomplished in children who are hypersensitive to foods such as egg. By feeding carefully adjusted increments of this, it eventually may be well tolerated.

An interesting biological feature of loss of sensitivity is its relation to the age of the individual. Stuart[41] has shown that up to the age of three years, hypersensitiveness is restricted chiefly to foods, rather than to inhalants, but that food allergy is largely outgrown by the age of seven when inhalants almost solely become the offending agents. Finally, there is a tendency for hypersensitiveness to become lost as individuals grow older.

In bacterial allergy, it is assumed by some that the use of specific vaccines causes desensitization. This is indeed doubtful and the process is easily confused with one of presumed immunization against the invading organisms. In this connection, the beneficial results from the use of autogenous vaccines often differs but little from those observed with the employment of non-specific substances. Injection of stock vaccines of staphylococci and of typhoid bacilli, tuberculin, solutions of inorganic sulphur and peptone have all given beneficial results in asthma, similar to those observed with autogenous vaccines. There is little doubt of the efficacy of these non-specific substances in this condition but their action is not understood. It is assumed (Auld[42]) that in some way they disturb temporarily the colloidal balance of the body and thus affect vagus tone, but thus far the justification for their use is purely empirical.

In conclusion, it should be emphasized that the immunological study of allergy becomes most difficult because the condition is restricted essentially to man. Various experiments on animals have been reported but it is doubtful whether the symptoms elicited and the mechanisms underlying them are truly those of allergy. For instance, several observers[43,44,45] have claimed to have reproduced bronchial asthma in guinea-pigs by sensitizing such animals and then causing them to inhale the specific antigen. In this way bronchospasm which simulates asthma may be reproduced. Recently, however, it has been shown definitely[46] that with such experiments, the underlying process is that of anaphylaxis and differs in no way from the mechanism elicited when such antigens are injected into the blood stream.

For a more detailed discussion of the immunological aspects of allergy, reference is made to the works of Coca,[47] Doerr[48] and Zinsser.[49]

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CHAPTER VI.

THE CLINICAL ASPECTS OF BRONCHIAL ASTHMA.

INCIDENCE.

It is extremely difficult to estimate the occurrence of bronchial asthma. It is not a reportable disease and its distinction from other types of dyspnea with wheezing such as occurs in chronic bronchitis, is not often made. Comparatively few patients with bronchial asthma enter hospitals and, consequently, estimations must be made from statistics such as those of the Army Medical Service, industrial insurance and life insurance. However, these deal with selected groups, mostly males, and do not account for children and adolescents which form a large class of asthmatics, nor are non-employed women represented. This becomes a problem for statisticians. Few extensive studies of the subject have been made. Isserlin,[1] from records of compulsary insurance statistics in Germany, estimated that in the year 1924 there were 500,000 cases of asthma in that country. Dr. Frederic Hoffmann,[2] the statistician, maintained in 1926 that there were about 500,000 cases of asthma per year in the United States. He found the ratio of males to females affected to be 26 to 21, and the mortality-rate 20 per 1,000,000 population. This, in England and Wales, is 54 per 1,000,000. These figures, of course, are approximate and probably too high, as all types of asthma are included. On the other hand, bronchial asthma is by far the most common type, and its total incidence doubtless is large.

In contrast to the low mortality-rate, the disability from asthma is great. There are as yet few collected statistics concerning this. Hoffmann estimated that in this country there are 13,000,000 days lost per year because of it. The

disability depends largely upon complicating organic changes such as chronic bronchitis and emphysema which will be discussed in conjunction with these lesions.

CLINICAL HISTORY.

Heredity.—In distinguishing bronchial asthma from conditions which simulate it, certain features of the clinical history are emphasized. The importance of heredity has been stated. Spain and Cooke[3] studied 462 cases of hay-fever and bronchial asthma with positive skin reactions, and elicited a family history of asthma or hay-fever, two conditions readily recognized, as follows. In 51.1 per cent of their cases, there was a positive antecedent unilateral history; that is, either paternal or maternal. In 7.3 per cent the antecedent history was bilaterally positive; that is, positive on both paternal and maternal sides, which gives a total of 58.4 per cent. Data was obtained, also, on 115 normal individuals, and an antecedent family history of asthma or hay-fever was elicited in but 7 per cent of these. Cooke and Vander Veer,[4] in a previous study had found a positive family history in 48.4 per cent of their cases, and Adkinson[5] in 50 per cent of the 191 cases that she studied. Spain and Cooke combined their figures with those of Cooke and Vander Veer, and in this series, 549 families with 1889 children were represented. They estimated that of 153 children with a bilateral family history, 69.4 per cent would become hypersensitive, and that of 816 children with unilateral family history, 58 per cent would become so affected.

In eliciting a family history of asthma, the occurrence of other manifestations of allergy of which bronchial asthma is but one expression, is sought for. Hay-fever is purely an allergic representation and consequently has the same significance as bronchial asthma. Urticaria, eczema, and probably angioneuroti cedema may result at times from underlying conditions other than allergy, and consequently a family

history of their occurrence is suggestive but not necessarily significant of an antecedent strain. Spain and Cooke's figures indicate that in some 40 per cent of bronchial asthmatics no family history of asthma or hay-fever could be elicited. They explained this in various ways. Statistics in any large metropolitan clinic are derived from people of various nationalities and at times it is very difficult to get accurate information. Either the patient does not know of the existence of clinical allergy among his antecedents; or the allergy in the antecedent never was made manifest clinically because of lack of contact with the specific allergen; or the allergic condition was clinically so mild that it escaped attention. Then again, eczema, urticaria, vasomotor rhinitis and other conditions which are sometimes expressions of allergy were not included as antecedent expressions of hypersensitiveness. If these factors were all considered, the statistical incidence of hereditary asthma doubtless would be still greater than about 60 per cent, although the control cases might be increased also. Heredity, then, must be considered a most important factor in the differentiation of bronchial asthma from other types, particularly asthmatic bronchitis which is a common liability, and inquiries into antecedent allergic symptoms deserve careful attention.

Environment.—An individual who inherits a tendency to bronchial asthma is one who is potentially sensitive to one or more allergenic substances. Unless he comes into direct contact with these, asthma, in the great majority of cases, will not develop. Consequently, environment plays an essential rôle in the development and continuation of the disease. Locality has always been emphasized as having an important bearing on the determination of asthmatic attacks. Patients are sent to the mountains or seashore or to some particular climate which previously had proved beneficial in other cases. Most adults develop paroxysms from inhalation of dust particles of specific substances to which they are sensitive. Once the disease has become well established, and the bron-

chial mucous membranes have acquired a high degree of irritability, then any irritating inhalant such as cold air, fumes, wind, etc., may excite an attack. A locality then, most conducive to attacks would be a dusty one, particularly if this dust contain the specific substance to which the patient is sensitive. Patients with pollen asthma due to ragweed become relieved immediately after embarking on a sea voyage. This, however, is of no benefit to the one sensitive to feathers who sleeps on feather pillows on the ship. Bakers sensitive to wheat, teamsters sensitive to horse dander, drug handlers sensitive to ipecac, beauty parlor employees sensitive to orris root, develop asthma from inhaling these particles, and may be relieved when otherwise occupied. In Holland there is a volatile parasite which infests grain to which many individuals are sensitive. Those asthmatics who live in the lowlands and who sleep on native straw mattresses are particularly susceptible. The incidence of these cases in higher altitudes nearer Switzerland where grain is sown less, is very small as Storm van Leeuwen[6] has shown. He relieves these cases temporarily with great success by placing them in a chamber into which dust-free air is pumped. Leopold and Leopold[7] constructed a dust-free chamber similar to Storm van Leeuwen's and found that the most severe asthmatics obtain relief with no treatment other than remaining in the chamber, which is kept at an even temperature. Any such permanent locality would be ideal for asthmatics. The same consideration determines the incidence of asthma at various seasons. Most cases occurring only in summer are due to volatile pollens, and those of winter to other allergens, as well as to dampness, cold air and respiratory infections. In all probability, the latter induces paroxysms from the cough of bronchitis or, in some instances, from a bacterial sensitization. These influences from which an individual with an hereditary history of bronchial asthma should be protected, will be discussed further under the treatment of the disease.

Age.—Bronchial asthma is essentially a disease of the earlier years of life. The two most important factors that determine the date of the first attack, are the degree of sensitivity and the amount of contact with the offending allergen. Individuals whose inheritance comes from both parents are apt to have their first attack early, even in infancy when first weaned on cows' milk, or still earlier. These infants and children frequently are found sensitive to many allergens at the same time, particularly to foods. This makes their treatment difficult. Not infrequently, if placed on a diet of non-offending foods they develop a sensitivity to one or more of these. This fact suggests an explanation of the various ages of onset of asthma. A high degree of sensitivity may express itself after short contact with allergens, whereas a mild sensitivity may remain subliminal for many years. In Table I taken from Coke's[8] series, it is seen that most cases occur before the twenty-fifth year. Statistics by Rackemann,[9] Walker,[10] and Alexander, Luten, and Kountz[11] conform essentially to this.

TABLE I.—STATISTICS OF THE AGE INCIDENCE OF ASTHMA AND OF SENSITIZATION IN 1000 CASES (COKE).

Age of onset.	No. of cases.	Percentage.	Number sensitive.	Percentage.
0 to 5	298	29.8	238	80
5 to 10	113	11.3	96	88
10 to 15	64	6.4	44	68
15 to 20	61	6.1	37	61
20 to 25	70	7.0	34	48
25 to 30	81	8.1	48	60
30 to 35	77	7.7	31	40
35 to 40	64	6.4	29	45
40 to 45	53	5.3	15	28
45 to 50	40	4.0	9	24
50 to 55	35	3.5	4	11
55 to 60	24	2.4	3	12
Over 60	20	2.0	1	5

The comparatively early age of onset is a valuable factor in differentiating bronchial asthma from other forms.

Free Interval.—A most important and striking feature of true bronchial asthma is that in the early years of its appear-

ance, before complications have set in, there is a free interval between attacks when there is no detectable symptom. It is amazing to observe the symptoms of a violent paroxysm at night and the apparently perfect health in the morning when the chest may be entirely clear and the patient may undertake his usual activities, even strenuous exercise, without undue embarrassment. It is this fact, and the absence of organic lesions in postmortem studies of a few early cases, that led to the conception of asthma as a functional disturbance. Since asthmatic attacks are typically nocturnal, especially in the earlier part of the disease, one treats many cases, particularly those in a clinic, without ever having seen the patient other than in apparently good health. Consequently, great dependence is placed upon the clinical history, and any recorded improvement is made entirely on the observations of the patient rather than on those of the physician. As will be seen later, the two almost inevitable complications of bronchial asthma are emphysema and chronic bronchitis. As these develop, they cause more or less dyspnea on exertion, and cough. Consequently, the free interval between paroxysms gradually becomes less. The reduced vital capacity of the lungs in emphysema limits the amount of exertion that can be undertaken, and the cough from bronchitis may cause sufficient irritation to the sensitive bronchial mucosa to produce some spasm. As these symptoms progress they lead to an ever increasing incapacity for work and in the worst cases there is more or less constant wheezing, cough, shortness of breath on mild exertion as well as frequent paroxysms. The majority of cases of bronchial asthma that are seen for the first time, already have developed these complications to a more or less degree. In some, the symptoms of these sequelæ are far more prominent than those of the attacks, and only a careful history will reveal that at one time the disease was one of paroxysmal attacks with free intervals.

SYMPTOMS AND PHYSICAL SIGNS.

Prodromata.—Swelling and secretion from the mucous membranes of the nose explains the sneezing, which is a frequent prodromal symptom to an asthmatic paroxysm. Many of the earlier writers laid stress upon other prodromata such as headache, lassitude, frequent urination and digestive disturbances; and some of these, especially gastric symptoms, are still emphasized occasionally. The great majority of bronchial asthmatics have few symptoms preceding their paroxysms, and these are referable to the respiratory tract. The most frequent is a sense of oppression over the thorax, associated with wheezing. This is of the same character as that of a paroxysm but of less intensity and may cause little embarrassment until, as it becomes worse, a true attack develops. This wheezing and the sneezing mentioned above are the two most common immediate prodromal symptoms. A more remote one is a head cold. This, however, is often difficult to distinguish from a true vasomotor rhinitis unless it be accompanied by bronchitis. So many attacks are nocturnal with the patient awakening to find himself sitting up in bed and already in a paroxysm, that here, as well as in many diurnal spells, there are no antecedent symptoms.

Nocturnal Occurrence.—An interesting phase of bronchial asthma is its characteristic nocturnal occurrence. A patient may feel entirely well on retiring, only to awaken in the early morning hours with an attack well begun. In many cases these occur at no other times, and one may carry on his customary daily activities. There may be even several attacks during the night and none in the daytime. These paroxysms may be fully established on awakening and by the time the patient gains consciousness he may find himself sitting up in bed or even standing in an effort to breathe more freely. However, these patients occasionally may be heard to wheeze during the sleep preceding an attack. In cases associated with chronic bronchitis, it is often the cough that disturbs

sleep and the difficult breathing gradually follows. This seems to occur more frequently in the morning hours after an otherwise restful night. It is noteworthy that in those whose activities keep them occupied at night and who rest during the day, the process is reversed and they have their attacks during their resting hours. This tendency to nocturnal attacks has received many diverse explanations. Salter[12] believed that the voluntary nervous system has a certain amount of control over the involuntary system but that this control is relinquished during sleep. Another theory is that during sleep secretions accumulate which may stimulate the bronchi or cause the patient to sleep with his mouth open and thus inhale cold night air. The contention of Weinberg[13] based on animal experimentation, that during consciousness there is heightened action of the sympathetic nervous system whereas during sleep parasympathetic or vagus action becomes dominant, deserves consideration. As Grimm[14] pointed out, this theory is in keeping with the nocturnal frequency of gall-stone colic and other smooth-muscle spasms. The hypersensitiveness to feathers which is common, undoubtedly causes nocturnal attacks in many patients, as a change to floss pillows often brings relief.

Offset of Attack.—Although it is well enough established that an asthmatic paroxysm may occur when an individual who is sensitive to a foreign substance comes in contact with this under proper conditions, little is known about the offset of an attack. The earlier experimental work of Williams and Einthoven suggested that bronchospasm induced by electrical stimulation could not be repeated indefinitely as there was an apparent muscle fatigue. Schilling, on the other hand, who observed the immunological response to reinjected proteins in the lung capillaries and bronchi described in Chapter III, noted a restitution to a normal state within a few hours. He suggested, therefore, that asthmatic paroxysms are limited by the time it takes for the process of destruction of foreign material in the lungs. Whether or not these theories be correct, remains undetermined.

Dyspnea.—The most conspicuous symptom of bronchial asthma is the dyspnea. Both subjectively, and objectively, it is obstructive in type and thus differs from most other forms wherein there is freer access of air to the alveoli. Consequently, the comparatively slow respiratory rate in bronchial asthma due to the time elapsed for the propulsion and expulsion of air through the narrowed bronchi, is in direct contrast to cardiac, pneumonic and other dyspneas in which there is rapid breathing purely from insufficient ventilation. Although the site of obstruction lies principally in the smaller bronchioles which have little cartilage to limit the extent of muscle spasm, other parts of the bronchial tree probably participate in narrowing the air passages from within, through mucosal swelling. This has been observed in the bronchioles on pathological sections, and in the larger tubes by bronchoscopy during an attack.

A distinguishing feature of dyspnea caused by obstruction anywhere in the air passages, is that expiration is usually prolonged over inspiration. This is due to the fact that the forces which suck air into the lungs are greater than those which push it out. In asthma, both phases are greatly impeded and there is little pause between them. The powerful action of the diaphragm soon becomes diminished for, as will be seen, the lungs become greatly inflated as the asthmatic attack develops. The flexible part of thoracic cavity is the inferior portion, and as the lungs distend, they crowd the diaphragm downward toward the abdomen. As the diaphragm thus tends to flatten, its excursion becomes limited just as any muscle which is shortened has a smaller range of movement than when at its full length. This process is observed readily under the fluoroscope during a paroxysm. The highly illuminated lung fields are bordered below by the diaphragmatic shadow which has lost its dome-shaped appearance and presents as flattened arches which are almost immobile. Consequently, the accessory muscles of inspiration, particularly the scaleni, pectorals, sterno-

cleido-mastoids, and intercostal levators take a large share of the burden of inspiration. These raise the thorax and give the characteristic stooped appearance seen during an attack, and the breathing becomes essentially costal in type. Nevertheless, despite this diminution of inspiratory force, the expiration is prolonged over inspiration. The normal ratio between the two is 1.3 to 1.5 whereas during an asthmatic paroxysm it varies from 1.5 to 2.1 according to the observations of Mudd.[15]

The orthopnea of asthma probably is similar to that of other severe dyspneas, but in severe attacks it may be extreme, and the standing position is maintained for hours. Whether or not recumbency causes respiratory embarrassment from the weight of abdominal viscera against the diaphragm, is debatable. Nevertheless, Bohr[16] has shown that the vital capacity of the lungs is greater when standing or sitting than when lying, and an asthmatic during an attack will assume the position that will give him most assistance in breathing.

Signs in Chest.—During an asthmatic seizure, the lungs become tremendously distended with air, and an "acute emphysema" ensues. This is due, apparently, to the fact that as the expiratory forces are somewhat less than those of inspiration, not all the air taken in is expelled with each breath, and, consequently, there is a gradual accumulation in the alveoli, which cannot be pushed through the narrowed bronchioles. As stated in Chapter III, a similar experimental observation was made in guinea-pigs that suffered anaphylactic shock. In these animals, bronchospasm traps air in the alveoli to such an extent that the lungs become enormously distended, so much so, that they are almost white as if most of the blood were squeezed out of them. As the lungs of asthmatics inflate and push down the diaphragm, they may force the lower edge of the liver below the free costal margin and it can thus be felt, as has been emphasized by Sihle.[17] However, the possibility of hepatic engorgement

during an attack, which would account for an actual enlargement of the liver must be considered. The distention of the lungs gives rise to a boardy resonance on percussion, which extends inferiorly far below the normal limits of the lung borders. Moreover, it greatly obscures the areas of cardiac dulness so that percussion of the heart outline becomes very uncertain. The hyperresonance is usually uniform in distribution, and if there be any uninvolved areas, they become obscured by the over-resonant ones. The increased aëration gives the high-pitched vesicular murmur heard on auscultation.

The air which thus is forced through narrowed airways produces a high-pitched whistling sound, the wheezing so characteristic of asthmatic breathing. Dixon and Brodie, who, as stated in Chapter III, produced bronchospasm by stimulation of the peripheral stump of a cut vagus nerve, noted that the effect was accompanied by wheezing. Musical rales, even, were heard by them on auscultation, although these were due probably to simultaneous stimulation of the secretory fibers of the mucous glands. This wheezing is felt by asthmatics and it is interesting that they may complain of it before it is audible. Since it denotes bronchial constriction and often precedes a paroxysm, it becomes a warning to patients with asthma. When it appears, many will burn stramonium powders or take epinephrine or other antiasthmatic remedies to ward off an attack.

The rales heard during a paroxysm may be many and varied. Those characteristic of asthma are the rhonchi with their musical quality. Sometimes no others are heard. Usually coarse bubbling rales are audible also, especially if the attack occurs in the presence of complicating chronic bronchitis. The number, loudness, and character of the rales are determined by the amount and viscosity of the bronchial secretions as well as by the size of the air tubes in which the sound is created; their distance from the stethoscope; the amount of air in the lungs and the other physical

forces which modify thoracic auscultation. In the intervals between paroxysms, there may be no rales, or, in the earlier cases, only an occasional rhonchus may be heard. After a complicating chronic bronchitis has ensued, coarse, moist rales, scattered or at the bases, may persist.

On careful auscultation of the chest during an asthmatic attack it is occasionally noted that not only are the rhonchi unevenly distributed with certain areas sometimes free from them, but that the vesicular murmur may be likewise irregular in distribution, and louder on one side than another. This unevenness is more difficult to detect by percussion than by auscultation. Siegel[18] called attention to this irregular distribution of signs and suggested that the lungs were not uniformly involved during a paroxysm. Some years earlier Levy-Dorn[19] noted at times a marked difference in the radioscopic shadows of the two lungs during an attack. Staehelin and Schütze[20] reported that the minute volume of air in an attack is not less, but greater than that during the free interval. They suggested that the ventilation differs in certain portions of the lungs during a paroxysm, and that the areas less affected have a hyperventilation and overcompensate for those involved. This work requires confirmation but in conjunction with the other signs, it is suggestive that a mild asthmatic attack may not involve the lungs uniformly, an impression concurred in by Meakins.[21] This may be true especially in occasional cases where there is a unilateral vagus irritation, as from the stimulation of the nasal ganglion on one side. This, according to Chauveau,[22] and Brodie and Dixon, induces an unequal effect on the bronchi of the two sides.

Circulatory Phenomena.—During a paroxysm, there is more or less cyanosis, which sometimes is marked. This is particularly true in long-standing cases wherein there is a complicating chronic emphysema, with consequent cyanosis between attacks, which becomes exaggerated during a spasm. However, even in the earlier cases, a severe attack may be

associated with bluish lips which appear in contrast to the frequently associated pallor.

Meakins[21] studied the oxygen unsaturation of the arterial blood during attacks and found it always increased in contrast to values during the free interval. During severe attacks this increase was marked. Alexander[23] noted the same thing and during an intense paroxysm, a 30 per cent arterial oxygen unsaturation was noted. In some instances the increases were nominal, and this suggests again the possibility that not all of the bronchi may be involved in a given paroxysm and that there may be sufficient hyperventilation *via* the free areas to partially compensate for those obstructed. Direct spirometric readings during an attack are naturally very difficult to obtain accurately, for the patient will not tolerate anything that hinders his struggle for air. Consequently, there are few reliable reports concerning alveolar CO_2, and other direct estimations of lung ventilation.

Whether this cyanosis be due essentially to alveolar deprivation of an adequate quantity of air, or whether there be sufficient circulatory embarrassment during an attack to account for it requires a consideration of the heart. There is surprisingly little published information concerning the heart in bronchial asthma, although there is a large bibliography on "cardiac asthma" wherein asthmatic breathing occurs as a complication of heart disease. Even certain modern "Systems of Medicine" contain directly opposing opinions by competent observers as to the involvement of the heart in bronchial asthma, and the statement in one that it becomes affected early in the disease is contradicted by another which maintains that it is rarely damaged. One quite consistent opinion found in text-books is, that sooner or later the right ventricle becomes dilated and hypertrophied because of the complicating chronic emphysema. This is a difficult matter to determine, for postmortem reports of bronchial asthma are comparatively few and the emphasis is usually on a description of the lungs. Moreover, some of the

cases in which the heart was studied died of an intercurrent disease, and others obviously were not true bronchial asthma. Consequently, at the present time, information concerning the circulation in this disease must be derived largely from clinical observations. Alexander, Luten, and Kountz, studied 50 bronchial asthmatics in whom the disease was of long-standing—an average of over ten years—and found that the heart remained singularly free from damage. The noteworthy findings in this investigation were that the heart is rarely enlarged and often is comparatively small; there is an increased peripheral venous pressure which may rise 200 to 300 per cent during an attack; a tendency to low blood-pressure; and an absence of right-sided preponderance either by roentgen-ray or electrocardiographic studies, even during paroxysms. These findings do not conform to the recent publication of Kahn,[24] who by electrocardiographic studies alone, reported a right ventricular preponderance in 20 per cent of a series of 50 asthmatics. Kahn, however, failed to publish criteria by which the diagnosis of true bronchial asthma was made, and since several of his patients had elevated blood-pressures, a condition unusual in essential asthma, there is a question of the correctness of his diagnosis in some of his patients. Then again, the underlying cardiac lesion was judged solely from electrocardiographic studies wherein the indications of preponderence of either side of the heart are so easily influenced by extraneous factors such as deep respiration, and the position of the subject. Only a complete clinical study of the heart will reveal its state in bronchial asthma.

At the height of an asthmatic seizure, there is usually a pallor, a small rapid pulse, fall in blood-pressure and the patient complains of palpitation. The pallor is often marked. Since an asthmatic attack is due presumably to a vagotonic influence, one would not expect an associated pallor of the skin, for it is the sympathetic portion of the vegetative nervous system that controls vasoconstriction of the systemic

vessels. Stimulation of the parasympathetic or vagus element should induce flushing such as is seen after pilocarpine injection. An explanation for this peripheral blanching may be an actual decrease in blood volume brought to the skin capillaries. The small rapid pulse and fall in blood-pressure during an attack is suggestive of this and further inference is noted below.

Between their paroxysms individuals with bronchial asthma tend to have blood-pressures below normal values for comparative ages. It is exceptional to find pressures much increased. In the above series of 50 cases[11] only 3 had high systolic values—150 mm., 156 mm. and 170 mm., respectively. The average was 118 mm. systolic and 74 mm. diastolic and the average age thirty-nine years. Sihle[17] noted a fall in blood-pressure during a paroxysm, and this is readily confirmed on clinical observation. A distinction must thus be made between the pressures of an attack and those of the free interval. That bronchial asthmatics should have a tendency to constant low blood-pressures is in keeping with their associated vagotonia in which there is a tendency to relaxation of systemic vessels. Moreover, low blood-pressure is associated with status lymphaticus, a constitutional defect seen frequently in asthma as noted in Chapter III. On the other hand, the lowered pressure during an attack and a small rapid pulse may indicate an actual decrease in blood volume in the systemic vessels. Opposed to this thought is the fact that peripheral venous pressures are much elevated during a paroxysms, and to account for such a discrepancy, one must consider what takes place in the heart.

In 1908 Götzl and Kienböck, [25] observed 2 cases of asthma radioscopically and noted that the hearts were small. Then, between attacks, they found that when these patients took a deep breath and strained with the glottis closed—the Valsalva experiment—the hearts were seen actually to diminish in size during this process wherein the intrathoracic pressure was increased. These observations were confirmed by Alexander,

Luten, and Kountz who found that the same thing occurred in healthy subjects. During normal inspiration, the negative pressure in the chest assists in drawing blood into the right heart. Conversely, by straining and thus increasing intrathoracic pressure the venous flow to the right auricle is impeded. It was thus conceived that a similar process occurs during a paroxysm. The straining to force air out of the lungs is considerable, and there is a corresponding increase in pressure in the thorax. The column of blood returning to the heart thus becomes proportionately obstructed, and there is damming back into the venous channels. This is readily seen in the greatly swollen veins of the neck, and in the hand where the venous pressure may rise to 15 cm. of water from 5 cm. The quantity of blood entering the right heart would be diminished and, consequently, the left ventricular output would decrease with the consequent peripheral effects noted above, namely: pallor, rapid, small pulse, low blood-pressure and cyanosis. In an experimental study of the circulation of guinea-pigs during bronchospasm, Smith and Alexander[26] found the effective venous pressure in the right auricle decreased unless the bronchospasm became extreme, and this is presumptive evidence of decreased filling of the heart. Although the simulation of the Valsalva experiment appeared to play some part, the reduction of effective venous pressure seemed to be due, particularly, to a disproportion of the ratio between intrathoracic and intra-auricular pressures. During bronchospasm, the normal relationship between these pressures becomes greatly disturbed. Of particular interest, is the fact that in such an event, the right ventricle instead of becoming dilated and hypertrophied from overfilling, as is commonly supposed, would suffer just the opposite effect. A recent postmortem examination of a patient who died during an attack showed this to be true. There was essentially no dilatation or hypertrophy of the right ventricle and the heart was small; only two-thirds of its proportionate weight to that of the body. This decreased filling of the

heart also may account for the great rarity of death during attacks of bronchial asthma in contrast to those of cardiac asthma wherein there is underlying cardiac damage and pulmonary edema frequently ensues. If the theory of diminished cardiac filling be true, then bronchial asthma, in a sense, actually may spare the heart, an hypothesis which is in keeping with the remarkable freedom from detectable lesions in the cases reported in the above series. The clinical signs of decreased output from the left ventricle may conceivably be accounted for by obstruction to the blood flow in the pulmonary artery. In such an event one should expect evident hypertrophy and dilatation of the right ventricle, a finding for which there is little confirmation in the few cases that have come to autopsy (Chapter IV).

Sputum.—During an asthmatic paroxysm, as secretions accumulate in the bronchi, there is an attempt to expel them by coughing. This is usually ineffectual, for on opening the closed glottis, the expulsive force is weak, due to the obstructed airways. Moreover, the mucous secretion is very tenacious. Consequently, only a thin frothy material is expelled which is saliva, for the most part. As the attack subsides, this weak unproductive cough becomes stronger and more effectual, which gives evidence that the paroxysm is wearing off. Then, a more or less characteristic asthmatic sputum is produced and the patient breathes easier but may be quite exhausted from his efforts.

The secretion which is produced at the end of a paroxysm is typical of true bronchial asthma and is diagnostic of the disease, for in no other condition does such sputum occur. Before a complicating bronchitis has set in, this has an appearance as follows. The color is grayish-white, the consistency viscid and somewhat resembles raw egg-white but is not so homogenous and is somewhat streaky and lumpy. Often it is thicker and more gelatinous. It consists almost entirely of mucus and is very tough. If spread out in a Petri plate and viewed against a dark background, small grayish particles are seen. These are the "perles" of Laennec. When

these are shaken in saline solution, they unravel into filaments which, viewed microscopically, are found to be made up of mucus threads arranged spirally about a central core. The cellular elements seen in such sputum are principally epithelial cells, mononuclear blood cells and, of great importance, eosinophiles. Polymorphonuclear neutrophiles in the uncomplicated cases are comparatively few, and if the sputum be thoroughly washed before examination, no large numbers of bacteria are present. After a complicating chronic bronchitis has occurred, the sputum may appear muco-purulent. Spirals and eosinophiles may still be recognized but polymorphonuclear neutrophiles and bacteria become abundant. Charcot-Leyden crystals which occasionally are seen in pathological conditions other than asthma, have not the diagnostic importance of spirals and eosinophiles, a combination that occurs only in bronchial asthma.

The significance of eosinophiles has been discussed in Chapter IV. Clinically, although they are quite constant in the sputum, their numbers in the blood are very variable. One may find high values both in the blood and sputum, or they may be numerous in the sputum and not abnormally increased in the blood. Blood values at any given time probably represent the numbers in transport from the bone-marrow to the bronchi where, apparently, they are attracted. Consequently, daily counts may show considerable discrepancies in differential values. By special staining methods, eosinophiles may be found likewise in the urine. In uncomplicated cases, there are no abnormal numbers of other blood cells. Even during an attack, the red cells are not materially increased in spite of venous congestion. After a complicating bronchitis has occurred, a moderate leukocytosis is common.

VARIETIES OF BRONCHIAL ASTHMA.

There are many classifications of bronchial asthma, based largely upon immediate etiology. Thus, inhalant asthma and its subdivisions into pollen, epidermal and other dust

groups; food asthmas; infectious and reflex types have been described. They are classified also in seasonal groups; as allergic and non-allergic forms and still other varieties. Clinically, these classifications are useful in determining particular cases, and suffer only because of their length and because there is no universal acceptance of any one classification. For the purpose of clinical distinction, it becomes necessary to be thoroughly acquainted with the essential features of true bronchial asthma, and to be able to recognize it even after complications have dominated the picture. It has the following characteristics: There is a frequent family history of allergic manifestations, as well as a past or associated history of allergy. The age of onset is in the earlier decades, usually before thirty-five years. The attacks which may be preceded by sneezing or wheezing are paroxysmal and in the interval between them there are essentially no signs or symptoms. The onset is not ushered in by cough, but this is characteristic of the cessation of a paroxysm. Physical examination between paroxysms may reveal a partial status lymphaticus. The blood-pressure is rarely elevated. Pharmacodynamic tests with epinephrine and pilocarpine usually show a heightened reaction to each, thus indicating an increased irritability of both elements of the vegetative nervous system. Little bronchial sputum is produced during an attack, but its offset is accomplished by a gelatinous bronchial secretion containing spirals and eosinophiles with comparatively few neutrophiles and few bacteria. There usually is a blood eosinophilia but no leukocytosis. Skin reactions to allergens occur in the majority of cases. Roentgen-ray examination of the chest shows no lesions. Immediate relief from epinephrine is characteristic.

The majority of cases of bronchial asthma are complicated by chronic bronchitis and emphysema and sooner or later essentially all unchecked asthmas are followed by these complications. Under such circumstances, the underlying bronchial asthma becomes more difficult to recognize at

times, and is revealed largely through the history of the earlier stages of the condition. There may be a family history of allergic disturbances and an early age of onset. At first the attacks are paroxysmal and in the interval between them there are no symptoms. The free interval is of considerable duration, a month or six months or longer. Gradually the attacks come more frequently. They may or may not become more severe. Sooner or later cough becomes a prominent symptom. These patients complain of taking cold readily which "settles in the chest." During winter, especially, one such attack may shortly succeed another. At their height these are associated with paroxysms of asthma which may last for a day or two. In the summer there is often freedom from symptoms. As the disease progresses, the emphysema causes disabling symptoms, particularly shortness of breath on exertion. This, in its severe form, is so crippling that the patient becomes incapacitated for work involving any physical exertion. The cough may become more or less constant, and be induced by such irritants as cold air, dust, fumes, or exertion. This cough may initiate a paroxysm of wheezing, so that there may be several attacks during the day. Often the severity of the asthmatic paroxysms grows less and these are replaced by cough and mild wheezing. At night, attacks are apt to occur toward daybreak. The patient awakens with a coughing spell which develops into a paroxysmal asthmatic attack. Eventually, large amounts of sputum are produced and the attack ceases. Then, during the day there may be only wheezing on exertion and some cough. At times, the bronchitis improves and the patient may be quite free from symptoms for a month or six months, but relapse is very likely. Physical examination shows the barrel-shaped chest, the stooped shoulders and high clavicles of emphysema, the signs of which are revealed on percussion and auscultation. The chronic bronchitis may be detected by moist rales between paroxysms. Evidences of status may be present and the blood-pressure still

tends to be low. Epinephrine and pilocarpine give heightened reactions. The sputum is muco-purulent and usually abundant. Spirals and eosinophiles persist but there are masses of neutrophiles and bacteria as well. Both an eosinophilia and a leukocytosis may be found in the blood. Skin reactions are still positive, but as the patient reaches the later decades, these tend to disappear. Roentgen-ray shadows show the low diaphragm, wide rib spaces and hyperilluminated lung fields of emphysema. Peribronchial thickening with fan-shaped shadows extending from enlarged hilæ well out toward the periphery of all lobes, presents a striking picture. Signs of diaphragmatic adhesions are common. Epinephrine injections relieves the wheezing but the cough persists and may require sedatives.

Finally, another variety must be considered. This includes asthmatics that probably are hypersensitive to bacterial products. The probability of hypersensitiveness to bacteria is discussed in Chapter V. Much has been written about this type of allergy and its occurrence is now commonly accepted. Direct evidence of bacterial hypersensitiveness in a given case is often difficult to establish, for skin reactions of the immediate type, to bacterial products are uncommon. Moreover, when they do occur with stock allergens, the corresponding organisms cannot always be found in bronchial or other lesions. Another unconventional behavior of bacterial allergens is their failure to evoke the general reactions that occur when other allergens are given in large doses. Instead of vasomotor rhinitis, urticaria and angioneurotic edema, all of which are expressions of the lesions of allergy, an overdose of bacterial products causes general febrile reactions. In both instances asthma may occur.

Clinically, there are grounds for belief of the existence of bacterial asthma. Not infrequently, the first attack follows pneumonia, or influenza, or pertussis. The possibility that the bacteria responsible for these infections induce a hypersensitiveness in those predisposed because of an inherited

tendency to allergy is quite likely. Then again, one occasionally sees patients with asthma and coincident infections in whom the asthma appears to be influenced in proportion to the severity of the infection. This is exemplified in the relief from attacks occasionally obtained by drainage of infected paranasal sinuses and treatment of similar lesions elsewhere. The intractability of many cases in which a chronic bronchitis is superimposed upon an asthma, may be due to the fact that a sensitivity to the bacteria in the bronchi develops, and this is not unlikely. This phase of the subject is receiving much attention at present. Bacterial asthma may resemble clinically either the uncomplicated variety, or if the infection be in the bronchi, it is quite like asthma with bronchitis.

Very occasionally one sees patients with typical asthmatic paroxysms but without evidences of allergy. Attacks may occur during pregnancy, menstruation, and emotional stress. Such asthma has been classified as "reflex," "nervous," etc. It is believed that these individuals are highly vagotonic, and that an asthmatic paroxysm is an expression of excessive vagus stimulation from non-allergic influences. Such cases are quite rare, and are identified by the absence of allergic signs such as an allergic history, skin reactions and sputum eosinophilia.

DIFFERENTIAL DIAGNOSIS.

Asthmatic Bronchitis. — The differentiation of bronchial asthma from other asthmas is not difficult if the patient be studied between paroxysms. Asthmatic bronchitis is the condition most commonly mistaken for true asthma. Since this is merely a particular expression of a severe bronchitis and as chronic bronchitis is a common liability, then a family history or past history of associated allergy is rarely obtained. A chronic bronchitis of such severity, which usually is associated with advanced emphysema is far more apt to occur later in life, and the age of onset is seldom in the early decades.

The constant prodromal symptom is cough which is severe and may be incessant. As this becomes more violent, wheezing sets in which may attain such severity that an asthmatic paroxysm is simulated. Hence there are paroxysms of cough followed by asthma rather than paroxysms of asthmatic breathing followed by cough. There is no free interval and the signs of bronchitis and emphysema are persistent. There is no increased incidence of status in this group and the blood-pressure is normal and, not infrequently, elevated. Injections of epinephrine and pilocarpine give normal pharmacological responses. The sputum usually is profuse and its production precedes an attack and likewise is coughed up during one. It is discolored, yellow or green, purulent, and contains no spirals or eosinophiles, but is loaded with neutrophiles and bacteria. There is no eosinophilia and a moderate leukocytosis is common. Skin reactions to allergens are rarely obtained. On roentgen-ray examination of the chest, signs of emphysema and of bronchial infection are seen. The heart is normal in size or there may be left-sided enlargement. Epinephrine and other antispasmodics may partially relieve the wheezing, but the cough persists.

Cardiac Asthma.—There is a type of asthma that occasionally occurs with hypertensive heart disease. This is known as cardiac asthma, and resembles bronchial asthma in that the attacks are paroxysmal and usually occur at night. Moreover, during a paroxysm, the signs in the chest are entirely like those of bronchial asthma. The condition is indicative of serious myocardial damage and an attack not infrequently ends in pulmonary edema. The absence of signs of allergy and the associated indications of cardiac disease establish the true diagnosis. The condition is comparatively infrequent but is a distinct clinical entity.

Other Conditions.—Renal asthma is very uncommon. Here, again, there is a typical asthmatic paroxysm with wheezing and the presence of musical rales. It occurs in the terminal stage of chronic nephritis, and is seen only with uremia. Its mechanism is entirely unknown.

Very occasionally conditions causing tracheal obstruction may simulate bronchial asthma. This may be true particularly of aneurysm of the innominate artery. For some reason not understood, the aneurysm may exert inconstant pressure on the trachea and the patient therefore may exhibit periodic attacks of obstructive dyspnea which resemble those of paroxysmal asthma. A careful examination of the chest should reveal the distinction although in a case recently seen, the diagnosis was made postmortem.

Patients with wheezing and difficult breathing sent to asthma clinics are found occasionally to have emphysema, obesity, cardiac disease, bronchopneumonia and tracheal obstruction.

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CHAPTER VII.

THE COMPLICATIONS AND PROGNOSIS OF BRONCHIAL ASTHMA.

There are two facts of significance concerning the complications of bronchial asthma. The first is, that essentially all asthmatics in whom paroxysmal attacks persist for any considerable length of time develop chronic emphysema; and the second, that the complications of asthma rather than the attacks themselves contribute most of the disability of the patient. The complications, insofar as structural changes are concerned, are limited to the respiratory and circulatory systems.

EMPHYSEMA.

That asthmatics develop emphysema with its attendant thoracic deformity, is an old observation and was mentioned by Aretaeus.[1] Statistics indicate that this complication is almost inevitable in long-standing asthma. Salter,[2] who made the first large compilation of cases, demonstrated this fact and elaborated upon the presumed mechanism of the structural changes in the chest. His statistics have been repeatedly confirmed. Reference is again to the series of Alexander, Luten, and Kountz[3] wherein 50 patients whose asthma had lasted five years or longer were studied. Particular attention was paid to the attendant emphysema which occurred in all and which was so striking, that in but one case did the vital capacity between attacks approach the estimated normal value for the individual.

The reason why emphysema should follow repeated asthmatic attacks so constantly is at present a subject for speculation. No experimental data is available. It is presumed, however, that repeated straining against obstruction to

expiration may cause chronic stretching of the alveoli. This explanation is employed by some to account for the emphysema seen in glass blowers and players of wind instruments, in whom repeated pulmonary inflation seems to lead to permanent distention. In support of this theory are the interesting observations of Mohr and Staehelin[4] who found that in untrained subjects, violent exercise or unaccustomed physical labor is followed by an acute emphysema which may persist for days.

Our knowledge of the pathogenesis of emphysema is extremely limited, no matter under what circumstances it may occur. Many theories have been advanced to account for its development, such as a congenital lack of elastic tissue in the lungs (Hansemann[5]); back pressure on the alveoli from forced expiration (Volhard,[6] Plesch,[7] Raither[8]); loss of elasticity from chronic infection (Tendeloo[9]); and several other theories which are no longer tenable. Jagiç, and Spengler[10] have recently remarked that many of the mild transient dyspneas such as are seen in overexertion and in acute bronchitis, are associated with more or less bronchospasm, a contention which they believed proven by the immediate relief which they were able to give by injections of epinephrine. So impressed were they by these observations, that they ventured to assume that all emphysemas not due primarily to a deformed thorax or to senile changes in the tissues have their origin in an underlying bronchospasm. Whatever may be the mechanism that underlies the development of emphysema in bronchial asthma, it is important to consider that probably it has a different origin from the emphysema seen in arteriosclerosis and senility.

Once emphysema has become well established, there is a definite alteration in the air levels of the lungs. Since the diaphragm is pushed down and the lungs, whose elasticity is diminished, are in the position of inspiration, only relatively small excursions can take place. Hence the midpoint of breathing is changed and the residual air becomes

increased. The limitation of respiratory excursion reduces the vital capacity and this reduction may be used as a rough index as to the degree of emphysema present. It is interesting, that in hyperinflation of the lungs after unaccustomed work, Mohr and Staehelin noted that the vital capacity is normal, and they state that it appears doubtful, therefore, if one should consider an increased volume of the lungs with a normal capacity as true emphysema. They believe that it represents the beginning of a true emphysema, but that the elasticity of the lungs under these conditions has not, as yet, been influenced to such a degree that the capacity for excursion is definitely limited. The same consideration must be applied to the early paroxysms of bronchial asthma where hyperinflation of the lung occurs. In chronic emphysema, the vital capacity may be markedly reduced, even to 1 liter or less. This reduction and the associated change in the mid-position of the lung probably accounts in large part for the shortness of breath that occurs in emphysema. Mohr and Staehelin state that the diminution in vital capacity, in general, is roughly parallel to the dyspnea experienced by emphysematous individuals on mild exertion.

The development of emphysema with consequent limitation of exertion is the cause of the greatest disability which chronic asthmatics suffer. At times the emphysema becomes so extreme that the patient may be totally and permanently incapacitated for physical labor. Certain of these patients may improve considerably under treatment, not only insofar as their paroxysms are concerned, but also in the diminution of their emphysema, as measured by an increased vital capacity. In view of the fact that chronic emphysema is caused by structural changes in the lungs, these cases are difficult to explain. Siebeck[11] found that spirometry is an unsatisfactory method to measure improvement, inasmuch as the mixture of inspired air and residual air is probably incomplete and therefore inconstant. This supposition is

confirmed to some extent by the variation in size of the air spaces in anatomical sections of emphysematous lungs. Careful observation of lung borders and circumference measurements of the thorax convinced Siebeck that some of his cases improved under treatment. He suggested that the bronchitis which is usually present in chronic emphysema may hinder the ventilation of certain areas of the lungs, and that the improvement observed may have resulted from lessened bronchial inflammation. Another possible explanation of the improvement noted during the treatment of these patients with chronic emphysema, would depend on the assumption that the myocardium is affected in such cases and that as the heart becomes stronger, the breathing improves. Only in advanced cases of emphysema following asthma, however, is there definite evidence of myocardial damage.

The effect of chronic emphysema upon the character of asthmatic paroxysms has been the subject of some discussion. Grimm[12] maintains that when emphysema is pronounced, the attacks are not so severe, and he accounts for this by the assumption that as the lungs become distended, the bronchi likewise stretch out so that their lumen is mechanically widened. Sonne[13] made this observation on anatomical specimens of emphysematous lungs and found that the width of the bronchi paralleled the degree of lung inflation. He assumed that emphysema, by widening the bronchi, plays a protective rôle in asthma. These observations could not be substantiated in the sections from cases of fatal asthma with emphysema described by Kountz and Alexander.[14] Although some of the most intense and prolonged paroxysms occur in old asthmatics, it is a clinical fact that many who develop chronic emphysema have attacks which are less severe in contrast to their earlier ones. A plausible explanation for the decrease in severity may be derived from the fact that as allergic individuals grow older, their specific hypersensitive-

ness tends to decrease. Their paroxysms would consequently become less severe and the symptoms of their emphysema would eventually constitute their chief complaints.

As a result of chronic emphysema, there is usually a cyanosis which, except in most advanced cases, represents derangements of the respiratory rather than of the circulatory mechanism. The studies of Blumgart and Weiss[15] who measured blood flow through the lungs in patients with emphysema, are of considerable interest in this connection. They injected a radio-active substance in the vein of one arm and measured the time it took to detect emanations in the other arm. They found no retardation in the speed of flow except in cases far advanced. When an asthmatic paroxysm supervenes upon chronic emphysema, the cyanosis may become very marked.

THORACIC DEFORMITY.

Another direct effect of chronic emphysema is the characteristic thoracic deformity. This results in a kyphosis of the upper spine and a lifting of the clavicles which eventually give chronic asthmatics a short-necked, stooped appearance. The antero-posterior diameter of the chest is increased, and the anterior deformity may vary from a rounded to a pigeon-breasted contour. Hyde Salter[16] was much interested in the mechanism of the kyphosis and he accounted for it by the assumption that the distended lungs exert pressure upon the anterior surfaces of the upper intervertebral disks, which, he thought, become partially absorbed and cause that portion of the spine to fall forward. Moreover, some of the muscles, especially those of the back, which are brought into action during obstructed respiration as accessory muscles, lose their function of supporting the spine. This conception requires proof, and no other explanation based on experimental work has been found.

CHRONIC BRONCHITIS.

Coincident with the development of chronic emphysema in asthma, one usually finds evidence of a chronic bronchitis. This, moreover, is believed by some to precede emphysema and to be a direct cause of it. The disabling symptom of chronic bronchitis, is cough. In chronic asthma, the bronchial mucous membranes appear particularly irritable not only to foreign matter, but even to the local disturbances induced by cough itself. Consequently, if the cough be at all severe or prolonged, a true paroxysm may ensue. Salter[17] explains such attacks by the assumption that the inflammatory process of chronic bronchitis contributes to narrowing of the bronchi which are more prone to contract since the bronchial musculature is hypertrophied in this stage of the disease. Clinically, the free interval between attacks of asthma is superseded by coughing spells which may be extremely distressing. The cough in itself may provoke asthmatic paroxysms, and so the attacks become more frequent. Consequently, any factors which improve the bronchitis will usually improve the asthmatic manifestations. This explains why patients with asthma and bronchitis are so often better during the summer months, or after a change to a warm equable climate. It must be remembered, however, that the underlying cause of the paroxysms, namely, a specific hypersensitiveness to some allergen, usually still exists, and that by improving the bronchitis, a restitution to the condition of uncomplicated asthma may be approached, depending largely upon how crippling the attendant emphysema will have become. The allergic influence may gradually diminish or, on the other hand, a bacterial sensitization may develop from the chronic bronchial infection. All these considerations tend to modify any fixed expectancies, and each case must be worked out separately.

If the bronchitis remains unchecked, a variety of pulmon-

ary lesions may result. The most frequent are permanent peribronchial sclerosis, hyperplasia of the lymph nodes at the hilus of the lung, and adhesive pleurisy. Less often, bronchiectasis ensues; rarely lung abscess. Bronchopneumonia is probably more frequent in old asthmatics than is recognized. This is often very difficult to determine because the pulmonary hyperresonance obscures underlying dulness. The loud vesicular breathing over the emphysematous areas may render detection of the changed breathing of consolidation almost impossible, particularly if many rales be present. Roentgen-ray shadows likewise become less clear through the hyperventilated lungs. The two distinguishing signs of bronchopneumonia with asthma, are the hyperpyrexia and leukocytosis. It has long been a common observation that asthmatic paroxysms often disappear completely during bronchopneumonia, not only in the febrile period, but for days or weeks thereafter. Relief has also been observed after measles, influenza and other fevers. It seems that an elevated temperature alone may induce relief. This is indicated by a recent observation on a patient with asthma. On elevating his body temperature to 38° C. by means of diathermy, his attacks ceased.

Chronic bronchitis is most readily detected by the history of cough preceding asthmatic paroxysms, coarse rales heard on auscultation, and by roentgen-ray and sputum examinations. Details of these are given elsewhere.

It is of interest to consider the bacteria usually found in the sputum of asthmatic patients with bronchitis. These, as stated previously, have been studied by Walker, Rackemann, Cooke, and Thomas and Touart and from their reports there is no evidence of any single predominant organism. Moreover, the mere recovery of bacteria such as Staphylococcus albus, Micrococcus tetragenous, Micrococcus catarrhalis, and others of the Gram-negative cocci, is by no means, indicative that these are responsible for symptoms. Sputum examinations must be made with careful technique and only

cultures of washed sputum which show organisms in large predominance may be considered to have a causal relationship.

EFFECT OF ASTHMA ON THE HEART AND CIRCULATION.

In any study of the effect of long-standing asthma on the cardiovascular system, the presence of a complicating emphysema must be considered. It was pointed out in the preceding chapter that there is some evidence to indicate that the asthmatic paroxysm itself, except for a temporary partial asphyxia, has little damaging effect on the heart. Moreover, the available postmortem reports of cases of long-standing asthma and emphysema do not show any particular lesion in the heart and none has been revealed on clinical investigation.

In chronic pulmonary emphysema on the other hand, it has long been known that there develops an associated hypertrophy and dilatation of the right ventricle. This, presumably is the mechanical result of increased pressure in the pulmonary artery which in turn is due to partial obstruction of blood in the proximal pulmonary circuit. The chief points of obstruction are the capillaries, narrowed and destroyed by the long-continued lung inflation, a fact which was shown by Isaaksohn,[18] as early as 1871.

It is apparent, therefore, that the emphysema accompanying bronchial asthma is not associated with the same structural changes that are found in other types. For instance, many cases of emphysema are associated with arteriosclerosis which appears later in life. In these patients, the heart frequently shows pathological changes. Arteriosclerosis, however, is not a part of the general picture of bronchial asthma nor is it one of its common sequelæ. This is in accordance with statistical evidence, despite clinical impressions to the contrary.[19,20] Again, Hansemann[5] emphasizes the contention that in most cases of emphysema, the

lungs are congenitally weak due to their inability to withstand heightened intra-alveolar pressure. In these cases, there is a defect in the elastic tissue. If this theory be applied to asthmatics, they must have congenitally weak lungs, an assumption which, at the present time, is not tenable.

The emphysema complicating bronchial asthma may not be uniform in its distribution. In such cases, postmortem findings have shown some portions of the lungs to be markedly inflated, and other portions to appear quite normal.[14,21] Under these conditions, the total obstruction to the pulmonary flow may not be sufficient to raise the pressure in the pulmonary artery. According to the experiments of Lichtheim,[22] to accomplish such rise in pressure, apparently a large portion of the pulmonary circuit must be obstructed. He tied off considerable areas of lung tissue without any rise in the pulmonary arterial pressure. Kretz[23] recently studied the problem of the effect of emphysema on the right heart, and he pointed out the difficulties of getting true values of vascular pressures within the closed thorax. These values change constantly with respiration and at any given moment the intrathoracic pressure would be distributed evenly upon the thoracic viscera. Kretz concluded that there is not sufficient evidence to assume that the presence of emphysema alone, would cause right ventricular hypertrophy. As has been stated, the studies of Blumgart and Weiss showed a retardation of blood flow through the lungs only in advanced emphysema.

Whatever be the underlying defect which allows emphysema to develop, there is little doubt that with extreme lung inflation which is prolonged over a period of years, there can be some increased strain upon the right heart, even in bronchial asthma.

At the present time, then, it is reasonable to assume that the emphysema associated with long-standing asthma does not as a rule particularly damage the heart, since clinical investigation and postmortem studies bear this out. On the

other hand, in this condition, the peripheral venous pressure has been found to be raised[3] and this is further increased enormously during an asthmatic paroxysm (Chapter IV). Recent experiments[24] indicate that the rise in intrapleural pressure and the partial asphyxia associated with bronchospasm cause a marked rise in peripheral venous pressure. The same effects, to a lesser degree are simulated by emphysema. It is quite possible that such a peristent partial venous stasis may account for the subcutaneous edema occasionally seen in advanced cases of bronchial asthma. This sign, together with the dyspnea on exertion and the cyanosis, each caused by emphysema, simulates the picture of cardiac decompensation. Without doubt, many asthmatics with these manifestations are treated for failing hearts, and they are responsible for the age-long misconception that heart failure is the common consequence of asthma.

The other complications of bronchial asthma are referable to the nose. Polyps are found frequently, but whether they are caused by asthma or precede it, is open to question. Since the lesions of the nasal mucous membranes of asthmatics apparently are similar to those of the bronchial mucosa, it may be presumed that nasal infection should occur as commonly as bronchial infection. This may account for the high incidence of sinusitis in chronic asthmatics.

PROGNOSIS.

The prognosis of bronchial asthma is notoriously uncertain. Asthma may manifest itself by a single attack, although this is unusual; or it may be continuous for many years; or attacks may disappear, only to recur, even decades later. There are two significant facts regarding the prognosis of asthma, namely, that death during an attack is exceedingly rare, and that the degree of disability is dependent largely upon the extent of the complicating emphysema and chronic bronchitis.

Almost one hundred years ago Andral[25] quoted "Asthma is a brevet of long life," a maxim which, he said, was then old. This conforms to the fact that not infrequently, one sees an adult patient who has had asthma throughout the greater part of his life. There are a few recent case reports in which death occurred during an attack. Hoffmann reported that the estimated mortality-rate in asthma in the United States during the year 1925 was about 2500 cases or approximately 1 per 45,000 population. This is in contrast to the estimated incidence of about 1 case in every 200 population in the same year. In the 2500 deaths, asthma was recorded either as a direct or contributory cause, and as no differentiation of the type of asthma was made, there is little doubt that a great many were cardiac asthma rather than the allergic form.

In accordance with the relative frequency of asthma, the degree of disability is great. Since chronic emphysema is a constant complication, its effect on the patient is usually far more crippling than the paroxysms during the earlier stage of asthma which are of but short duration. The majority of bronchial asthmatics who present themselves in a hospital or clinic show evidences of emphysema. Just how much disability results, as measured by such standards as days lost from work or school, is not known accurately.

In order to obtain some information as to the relation of the complications of bronchial asthma to permanent disability as measured by lack of response to treatment, a series of 200 cases were studied by Alexander and Zeek. These patients were selected from the asthma department of the Cornell Clinic and only those who had been under treatment there for at least one year, were included in the study. Two facts were determined, namely, whether chronic emphysema and bronchitis were present, and whether after treatment, there remained sufficient disability to interfere materially with the patient's occupation. Often, it was difficult to estimate the degree of disability which was evaluated by

such criteria as loss in wages, days lost from work, school, etc. Eventually, these cases were classified as complicated or uncomplicated, and disabled or improved. Of these 200 cases, 69 were found uncomplicated, and of these all but 7 or approximately 90 per cent, improved under treatment. Of the 123 complicated cases, only 29, or less than 24 per cent, responded to treatment, the remainder continuing their disability.

These facts accord with the long-standing clinical observation that most of the disability of asthma occurs in the complicated cases. Moreover, since most patients with uncomplicated asthma respond to treatment, and since all chronic asthmatics develop emphysema eventually, it becomes evident that the favorable time to treat these patients is early in the disease. There has been much justifiable propaganda concerning the necessity of early treatment in tuberculosis, syphilis, and cancer, and the same principle applies to bronchial asthma. It must be looked upon as a chronic, progressive, crippling disease. If treated early, before structural lesions have occurred, the chance of improvement is far greater than after these permanent defects have become established.

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CHAPTER VIII.

THE TREATMENT OF BRONCHIAL ASTHMA.

Far more has been written concerning therapy in asthma than of any other phase of the disease. The number of so-called "cures" is legion. The temporary success of various forms of treatment becomes understandable when one considers that a paroxysm of asthma is essentially a functional disturbance due to increased vagus tone. Anything that diminishes vagus irritability may benefit asthma. As has been pointed out (Chapter III), the vegetative nervous system is influenced by various intricate chemical, physical and psychical forces, all of which are but imperfectly understood. Consequently, the intravenous administration of calcium, the application of radiation, and psychic hygiene, each may serve as a depressant on the vagus and thus prevent bronchospasm. Another therapeutic approach takes into consideration the fact that bronchial asthma is an expression of allergy, and treatment is directed toward the diminution of a specific hypersensitiveness.

DRUGS.

Epinephrine.—The successful therapeutic measures used to alleviate asthmatic paroxysms are confined largely to drugs. Many such antiasthmatics have been described, but the effective ones are few. The drug *par excellence* for the immediate relief of an attack is epinephrine. Its use in asthma was recommended first by Solis-Cohen.[1] As it acts by heightening the tone of the sympathetic portion of the vegetative nervous system, the opposing parasympathetic action or vagus "pull" is thereby overcome. Bronchospasm is thus released, and there is a shrinkage of the bronchial mucosa due to vasoconstriction of the arteries that

make up the systemic portion of the bronchial vasculature. The particular advantages of epinephrine are its potency and its almost immediate action. There are, on the other hand, certain disadvantages. The first of these is the necessary awkwardness of administration because of the fact that it is ineffectual by mouth and must be given hypodermatically. Another difficulty is the fact that epinephrine action may be of comparatively short duration and severe cases often require several injections during the course of an attack. In protracted cases it has been used several times daily for months. Recently Luckhardt[2] reported that the effect of a single subcutaneous injection could be repeated simply by rubbing the site of administration. In this way the drug, a considerable portion of which apparently remains localized, may be forced into the circulation at will. Should this observation be substantiated clinically, it will prove a most useful procedure. Epinephrine has certain by-effects which, at times, are very disagreeable. They are merely exaggerations of sympathetic irritability; nervousness, tremor, pallor, headache, and palpitation. Asthmatics are prone to be hypersensitive to epinephrine,[3] and its effect may become manifest with a small dose. Consequently, it is far better to use 3 minims of a 1 to 1000 dilution of the chloride rather than 8 minims or more which is the quantity usually prescribed for relief of paroxysms. In most cases, the smaller dose is sufficient. It is remarkable for how long a period epinephrine may be taken. Occasionally, one finds a patient who claims to have attained a tolerance to the drug so that it no longer becomes effective. There is some doubt as to whether this is a true tolerance, or whether, as is probable in many such instances, the paroxysms become more severe in intensity so that much larger doses are necessary. Very violent attacks may require as much as 2 or more cubic centimeters before they are controlled. Epinephrine is so effective that many patients learn to administer it themselves and are never without a bottle of it and a syringe.

Ephedrin.—Recently Chen[5] and his co-workers have proven the efficacy of ephedrin, an active principle of *ma huang*, which has been used as a therapeutic agent in China for several centuries. Its effect simulates that of epinephrine and the structural formulæ of each are closely related. The great advantage of ephedrin over epinephrine is its effectiveness when given by mouth. Under these conditions, its action may be prolonged for several hours. The dose is 25 mg. to 50 mg. and it may be given four or more times a day. Not only is it beneficial in asthma, but apparently it is useful in other allergic disturbances such as hay-fever and urticaria. Encouraging results in such cases have been reported by Thomas,[6] Piness and Miller[7] and by Gaarde and Mayturn.[8] Unquestionably, it is of benefit in some cases and deserves a trial. It is of particular use when hypodermic injections are not feasible. A mild and prolonged epinephrine effect makes ephedrin an excellent prophylactic remedy against paroxysms. Once these occur, epinephrine may be used to relieve them although a 3 per cent solution of ephedrin given hypodermatically also is effective. Ephedrin solution also may be employed as a nasal spray to reduce the boggy nasal mucosa so frequently found in asthmatics. In a certain percentage of patients the drug is not well tolerated because of its by-effects.

Atropine.—Another much used drug in asthma is atropine. This acts presumably by paralyzing the vagus nerve endings in the bronchi, although, as recently shown by Gasser,[4] it likewise may affect smooth muscle directly. Its administration to sensitized guinea-pigs prevents anaphylactic death from bronchopasm. Although, theoretically, it should be an excellent antispasmodic, actually it is not nearly as effective as adrenalin. This is probably because the dose usually prescribed, $\frac{1}{100}$ gr. or $\frac{1}{75}$ gr. is too small. Larger doses may be quite effective but cannot be repeated often.

Calcium.—Calcium, either as calcium chloride or calcium lactate has been used in bronchial asthma and hay-fever for

some years and with apparently good effect at times. It forms the basis of many proprietary remedies for asthma. The drug may be given by mouth, and is usually administered in doses of 3 to 4 gm. daily although much larger amounts have been advocated. Pottenger[9] advised its intravenous use in the form of 5 per cent calcium chloride solution. The effectiveness of this drug is uncertain and its action not clearly understood. Calcium is thought to act as a stimulant to the sympathetic nervous system and thus overcome vagus pull. Rittmann[10] found that calcium, like epinephrine, prevented bronchoconstriction in human bronchial muscles which were tested on their removal soon after death. The mechanism of the effect of calcium therapy in asthma is very involved and is not well understood, as no studies on ionizable calcium in the body are available.

Other Drugs.—One of the distressing symptoms of bronchial asthma is the effort to raise the thick sticky sputum which plugs the bronchioles. Once this is brought up, breathing becomes freer. Potassium iodide is a good drug for this purpose and forms the basis for many of the proprietary medicines that have enjoyed success as asthma "cures." It is very useful, and is best given in 5-gr. doses with 5 minims of the tincture of belladonna, and some simple vehicle. This mixture administered four or five times a day, is often effective in preventing the recurrence of paroxysms.

Stramonium fumes will sometimes relieve bronchospasm very quickly and with potassium nitrate (saltpeter) it forms the basis of asthma powders. These are burned and the smoke inhaled. This is frequently a simple and useful remedy, but many asthmatics find it too irritating. It apparently penetrates well into the smaller tubes, as its particles appear under the microscope as black specks adhering to the spirals in the sputum.

Many other drugs such as potassium arsenate, lobelia, and benzol benzoate have been advocated for the relief of asthma, but they are no longer considered useful. Cocaine

undoubtedly is of value and acts by reducing mucosal swelling. This action has been observed through a bronchoscope directly after its application to the bronchi. Even as a nasal spray, it may relieve attacks, although the mechanism involved here is not clear. Cocaine, greatly reduced in strength, forms the basis of a famous proprietary asthma remedy. So simple is its administration, that not infrequently one finds patients with an atomizer containing it in their pockets or handbag.

Morphine has been used extensively for the control of attacks but it should be strongly condemned for this purpose. Not only is the opportunity for habit formation great in such a chronic disease as asthma, but its use is illogical, for Jackson has shown experimentally that opium derivatives cause bronchospasm. There are comparatively few cases that cannot be controlled temporarily by epinephrine.

Oxygen inhalation is advocated as a useful measure to relieve cyanosis by Meakins,[11] but its effectiveness in asthma is questioned by Mudd.[12]

PROPHYLAXIS.

In discussing general measures in the treatment of bronchial asthma, perhaps the most important consideration is its prophylaxis. This is true because not only is prevention always more satisfactory than therapy, but, also, since asthma invariably progresses to structural changes in the lungs, protection against these processes can be accomplished only through avoidance of attacks. The present conception that most cases of bronchial asthma occur on contact with some foreign substance to which an individual is hypersensitive, points a way toward rational prevention. Every resource should be used to discover the offending allergen. To this end, there are several distinct methods of approach.

The history of a given case is often a most important adjunct. Not only may it suggest that an individual is

allergic, but it also may reveal several possible clues leading to the immediate cause of attacks. It is a matter of clinical experience that comparatively few allergens are responsible for paroxysms in the great majority of asthmatics. Consequently, it is customary to ask certain conventional questions concerning the use of feather pillows, the presence of household pets, the proximity to stables, the use of face powders or insect powders, etc. If such contact is established, skin tests are done with the allergen in question, and if these are positive, a strong suspicion that this is the offending substance, is justified. This will then be confirmed if attacks cease on avoidance of this contact.

Skin tests are a most important aid in diagnosis, provided they are correctly done and carefully interpreted. Multiple reactions, which are frequent, present difficulties. It has been stated that the presence of a positive skin reaction does not necessarily indicate sensitive bronchi, so that each reacting allergen must be investigated separately by attempting to establish a history of contact and by removing it from the patient's environment. In the presence of persistently negative skin tests, it becomes necessary to investigate by other methods. Offending foods may be searched for by restricting the diet for two or three days at a time when attacks are frequent. One or two foods such as tea and toast, or milk, may be given. If attacks persist, then all other foods save these are allowed. If food be a factor in persistent asthma it is likely to be one commonly eaten, and a diet free from milk, wheat, and egg is frequently successful and well worth trying. Each of these may then be allowed successively and changes in symptoms noted. More difficult to solve are the occasional attacks, especially in children. Here, some uncommon foodstuff is often at fault. Rather than perform a large number of skin tests in hopes of detecting this, it is better to await a subsequent attack and then to review every article of food eaten in the preceding twenty-four hours. Any suspicious allergen then may be tested for or cautiously administered.

The detection of inhalants in persistent asthma becomes a matter of investigation of a patient's environment, his home, and place of work. Some asthma clinics have trained workers who make such a survey. The character of pillows, mattresses, quilts and upholstery; the presence of powders and household pets; the proxmity to stables and the position of bedroom windows in relation to them; and occupational dusts, are all investigated. It is a painstaking, time-consuming, and often discouraging task but until some simpler method is offered, the successful prevention of most cases of bronchial asthma will depend on the ability to detect the immediate cause. Cooke[13] has found that, at times, when the specific inhalant cannot be detected in a given case, an extract of house dust will give a positive skin reaction. This dust may be collected from rugs, bedding, floors, etc., preferably into a vacuum cleaner, and extracted in the same way as an epithelial allergen (see Appendix). Often after a reaction from such composite material, the particular substance responsible for symptoms will be detected. An extremely interesting development of house-dust reactions has been the discovery that certain of these dusts collected from particular localities will give skin reactions not only in the inhabitant thereof, but in many other asthmatics. In some instances, treatment with such an extract has been successful.

In very many instances, not only does specific dust, but also any particulate matter through its irritation to the bronchial mucosa, cause symptoms. Storm van Leeuwen,[14] particularly, made a study of this, as has been mentioned, and found that in Holland, asthma is far more frequent in low-lying districts such as along river valleys than at higher altitudes where the air is clearer. He devised dust-free chambers and found that the severest cases would remain without symptoms in such an atmosphere, only to relapse on leaving it. Such dust-removing devices are constructed in dwellings there. Confirmation of Storm van Leeuwen observations is found in the results of Leopold and Leopold[15] who constructed a similar dust-free chamber and found that

patients soon lost their symptoms while remaining in it. If dust, however, was introduced into the chamber, asthma returned very quickly. Cohen,[16] likewise, has had success in asthma and hay-fever with a dust-removing device. Apparatus for making rooms essentially dust-free are now on the market.

It is a matter of common experience that most adults with bronchial asthma will lose their symptoms very quickly after entering a hospital where iron furniture, felt mattress and floss pillows are furnished. Thus, they have escaped apparently, the specific irritant in their usual environment. Under such circumstances, an effort is made to duplicate the hospital room at home, at least insofar as the bedroom is concerned. Rugs and draperies which catch dust are removed, the walls are rubbed down, the floors are oiled and if of soft wood, are repainted and the cracks filled, and unupholstered furniture is used. Proper bedding is substituted. Draughts, which carry dust from other rooms are avoided. Under this régime, many patients improve, particularly those in whom a history of freedom from symptoms when away from home, is elicited.

Patients with hay-fever and vasomotor rhinitis are potential asthmatics, for a hypersensitiveness of the lower respiratory tract to the allergens that cause symptoms in the upper tract, may develop. Consequently, it is most important that these patients be treated either prophylactically as outlined above, or by desensitization, as will be described. Patients with hay-fever often seek relief by going to a region where the particular offending plants do not grow. Thus, in ragweed pollinosis, relief is had by going abroad as this weed is an American plant, or into northern latitudes or to sufficiently high altitudes. This holds true particularly for children, in whom hay-fever is more likely to be complicated eventually by asthma than it does in subjects whose symptoms first appear later in life. Although, in these cases, such asthma at first is seasonal and periodic, the usual consequent bronchial infection may supervene.

Patients whose asthma is complicated by pronounced bronchitis which in turn tends to excite paroxysms, should receive adequate treatment for their bronchial infection. This differs in no way from the attention given to other cases of chronic bronchitis—medicinal, vaccine and climatic. The fact that such patients are usually better during the summer months is taken advantage of, and when possible, they are sent to equable climates where it is perpetually warm.

The rôle of remote infections in bronchial asthma has been discussed. A great deal of therapeutic abuse is practised on patients with such defects. Attention has been paid particularly to the upper respiratory passages. Tonsillectomy, turbinectomy, polypectomy, septum resections, antrum irrigation, upper sinus drainage and sphenopalatine ganglion injections are the most frequent procedures. In certain cases, some of these undoubtedly are indicated, but in no instance should relief be promised. As has been pointed out, there is distinct indication that a pathway exists between the sphenopalatine (nasal) ganglion and the vagus branches controlling the bronchial musculature. Consequently, pathological processes in the neighborhood of the ganglion may be foci of irritation. Should such lesions be present, their adequate treatment is indicated. The mere presence of a deflected septum or of a polyp in the nose does not constitute justification for correction insofar as asthma is concerned. Likewise, infections of the teeth, the genito-urinary and other remote organs may be treated because of their local indications, but their influence on asthma has not been established.

It is a matter of clinical experience that chronic bronchitis often follows chronic sinusitis, and consequently a definitely infected sinus in an asthmatic should be treated. Some of these cases may be difficult to diagnose, for one may find a thick secretion in the maxillary sinus which is mucoid in character and in which there are eosinophiles rather than pus cells. This exudate gives a shadow to roentgen-rays and cloudiness on transillumination and thus simulates

infection. A microscopic examination of the material obtained by suction will make the distinction.

When other means have failed, Sluder[17] has had frequent and striking success in checking asthmatic paroxysms by cocainizing the nasal ganglion. In these cases, the cause of attacks was probably a pathological process in the nose. The procedure is, therefore, a useful one but as it acts only as a vagus block, it does not alleviate the underlying cause, nor is it always permanent. The great majority of such injections do not strike the ganglion directly, but the effect is attained by infiltration of the tissues in the neighborhood of the ganglion. Its particular drawback is the difficulty of the procedure in other than skilled hands.

DESENSITIZATION.

It has been stated repeatedly, that asthmatic paroxysms develop in hypersensitive subjects after contact with a particular allergen. When this substance is known, symptoms may be prevented if contact is avoided, but in certain instances such avoidance is not possible. Asthma associated with hay-fever should be treated by desensitization to the offending pollen when escape to other parts is not feasible. The same holds true of horse dander, for there is usually enough of this in the dust of city streets to induce symptoms. Orris root, likewise, is difficult to avoid if an individual be highly sensitive, as he will come in sufficient contact with it in street cars, theaters and other places where women assemble.

Although man cannot be completely desensitized, he may be treated sufficiently to alleviate symptoms. There are various methods of procedure of which there are two particular distinctions. One deals with prophylactic and the other with phylactic treatment. Prophylactic treatment is applied in cases of hay-fever and, on the whole, is very successful, if properly carried out. Symptoms are thus

greatly alleviated and asthma prevented. In these instances, the date of first pollination of the offending plant being known, sufficient time is allowed for a course of injections before those pollens appear. The pollen extract is made as described in the Appendix of this book. This extract is standardized either by nitrogen content or by a ratio of the weight of dried pollen in grams to the number of cubic centimeters of extracting fluid. From such a stock extract, dilutions are made in multiples of ten. For instance, if the stock extract is 1 to 10, then this is diluted to 1 to 100, 1 to 1000, etc. Skin tests are done with the lowest concentrations until a distinct reaction appears. Thus, a dilution of 1 to 1000 may react but not one of 1 to 10,000. A safe method is to begin injections with the dilution which just fails to cause a skin reaction; in this instance, 1 to 10,000. This is sometimes checked by the ophthalmic test and if this be strongly positive, the next further dilution is used in the initial dose. This having been established, various time intervals between injections are employed, depending on the system used. One conventional method is to begin with 0.1 cc., then 0.2 cc., 0.4 cc. and 0.7 cc. are administered at five-day intervals. The same dosages are repeated with the next stronger concentration until a dilution of 1 to 10 is reached. After this, the dosage becomes 0.1 cc., 0.2 cc. and finally 0.3 cc., which should be given just before the expected date of pollination. Thereafter, an injection of 0.2 cc. of a 1 to 1000 dilution is often given once a week throughout the pollinating season. It is important that strong concentrations should be attained as pointed out by Caulfield.[18] Not infrequently, local reactions such as redness, heat, and swelling, and occasionally systemic manifestations with signs of hay-fever, also of urticaria, angioneurotic edema and asthma follow soon after an injection. On such occasions 0.5 cc. of a 1 to 1000 solution of epinephrine chloride is given as soon as possible, and repeated if necessary. The next injection should then be a repetition of the one that caused no reaction and the schedule

pursued. Occasionally, this must be modified to suit the occasion by using smaller increments.

Many modifications of this method are described. Some begin injections about six weeks before the expected season and administer them every forty-eight hours. Walker[19] finds best results when the intervals are not shorter than every five days. Brown[20] advocates giving injections once a week throughout the year. Phillips[21] recommends the intradermal rather than the subcutaneous administration of the extract, whereas Mackenzie[22] supplements the hypodermatic treatments with nasal sprays of the pollen extracts. Various commercial extracts on the market have particular schedules worked out for them. Concentrated extracts now may be purchased and one may make his own dilutions to any desired strength. About equal success is claimed for all these methods and it becomes largely a matter of choice.

Phylactic treatments are carried out in much the same way for pollens and other allergens where large quantities of these are present in the air. Again, several methods are advocated, once symptoms are present. Weak dilutions are used as the initial doses and may be given at frequent intervals. Vaughn[23] finds particular success with this method. With orris root, house dust, horse dander, etc., phylactic schedules are used. In the case of horse dander, further desensitization may be had by active contact with this material. The patient having had a course of injections may then enter a stable for but a minute or two, and again for longer intervals until he can tolerate that atmosphere for a considerable length of time. He may then ride or even currycomb a horse and so increase actively his tolerance to the dander.

In children who are intolerant to foods, desensitization by feeding may be accomplished. It is very important that this be done if the food be a common one, as is usually the case. Occasionally, the slightest amount of egg, for instance, may cause asthma, urticaria and other symptoms of allergy. Not only does this impose considerable dietary restriction from all egg-containing foods, but the child is in constant

danger of symptoms. The method of desensitization is based on the same principle as that of hypodermic injections. Egg-white is used in dilutions and the initial dose may be estimated from skin tests cautiously done, or, in the absence of these, by applying a drop on the tongue and noting any local edema. If this occurs, the presence of such a strong intolerance demands a weak dilution for the initial dose. A feasible schedule in such a case is to begin with 1 drop of a 1 to 1000 dilution given in an ounce of water. The dose is then increased by 1 drop after each meal until 15 drops are tolerated. A dilution of 1 to 100 is then used and the schedule repeated, and then again repeated with a dilution of 1 to 10, but in this instance doses are continued to 30 drops and then a teaspoonful after meals for a few days. After this, small bits of the white of a hard-boiled egg are given, and so on until a whole egg is tolerated. Then some egg-containing food should be given every day.

These methods of desensitization have limitations, particularly in that they are not permanent. In the instances of pollinosis, injections must be repeated usually every season, and in the cases of other allergens, unless contact be maintained quite constantly after desensitization is accomplished, treatments at times have to be repeated. Another particular disadvantage is the presence of local or general reactions, and occasionally patients are encountered in whom it is not possible to give adequate treatment because of a persistent reappearance of these reactions when stronger concentrations are used. On the other hand, desensitization is, on the whole, successful and of great advantage in those cases where the offending allergens cannot be avoided.

NON-SPECIFIC THERAPY.

Non-specific therapy in asthma, as pointed out in the beginning of the chapter is, at times, of distinct temporary benefit. Very little is known concerning the mechanism involved, and such treatment is purely empirical. Although

each non-specific agent that has been used has been more or less enthusiastically supported, it does not seem to matter a great deal which is employed, as all of them seem about equally successful.

Tuberculin.—Tuberculin has found favor in many hands. Storm van Leeuwen and Varakemp[24] maintain that in asthmatics treated with tuberculin, hypersensitiveness to allergens actually becomes reduced. They keep their patients in bed at the beginning of the tuberculin treatment and for the first injection use very low concentrations (1 to 100,000) of tuberculin which is given subcutaneously. At first it is administered every other day and later at wider intervals. These observers have noted improvement after the first few injections. The treatment is continued for many months. Of 150 patients so treated, they record 138 as cured or greatly benefited. Other similarly encouraging results with tuberculin have been reported by Frankfurter,[25] Bouveyron,[26] and Hekman.[27] The latter observer considers the treatment specific in that he believes that tuberculosis underlies the asthmatic process. Arjeff[28] failed to benefit asthmatics with tuberculin and Kämmerer[29] questions its usefulness.

Peptone.—Peptone has been advocated by Auld[30] particularly, as a beneficial agent in bronchial asthma. Its action in this disease is due, supposedly, to its influence on the balance of the colloids of the body, although just what adjustments take place is highly speculative. A particular commercial preparation ("peptone siccum") which presumably is free from intoxicating proteoses found in Witte peptone, is recommended. This is made up in a 5 per cent solution and administered subcutaneously and then intravenously. Marked beneficial results have been reported. On the basis of allergy, Miller[31] has used this formula in the treatment of migraine with distinct success. Larsen[32] and his co-workers, on the other hand, found this preparation highly toxic for some individuals and reported two severe accidents in 9 patients in whom it was administered intravenously, and its

use was, discontinued. It has not found much favor in this country.

Vaccines.—Vaccine therapy in asthma has many advocates. Walker, Rackemann and Thomas and Touart believed that a positive skin reaction, either immediate or delayed, indicated that the organisms causing such a response were specifically responsible for the paroxysms. Treatment was thus instituted with autogenous vaccines, with more or less success. For the most part, these were made from organisms recovered from the sputum. Koopmann,[33] likewise, reported success from the use of autogenous vaccines made from sputum and failure when vaccines from normal sputum were used. Solis-Cohen[34] devised an ingenious method of selecting proper organisms by planting sputum in a culture medium composed of the patient's whole blood. Under such circumstances only those organisms would grow to which the blood showed no immunity. Vaccine treatment in bronchial asthma is quite conventional in that small subcutaneous doses are given at first with gradually increasing increments. Rackemann found that the best results were obtained after each dose that gave a local redness and swelling associated with a febrile reaction.

Larsen and his associates discovered that results quite as successful were obtained by the use of non-specific vaccines. In view of Rackemann's observation that a febrile reaction is beneficial, it is quite probable that vaccine treatment in asthma is non-specific therapy. Gottlieb's[35] work also tends to confirm this. He found that *B. coli* gave positive reactions not only in asthmatics in whom infections occurred, but also in those sensitive to inhalants in whom treatment with a vaccine of this organism was successful. Larsen and his co-workers used a stock vaccine of Staphylococcus aureus and albus containing 500,000,000 organisms of each to the cubic centimeter. They gave 0.1 cc. as the first dose, 0.2 cc. as the second and thereafter 0.3 cc. These were given at three- to four-day intervals. It was found that

larger doses tended to induce asthmatic paroxysms and that the best results were obtained in the absence of local or general reactions. Fifteen injections constituted a course of treatment. Typhoid vaccine did not seem to give good results when given subcutaneously. Vander Veer[36] had the same experience with this vaccine. Given intravenously, however, typhoid vaccine causes hyperpyrexia and, as a rule temporary cessation of paroxysms for a short time thereafter.

Other Non-specific Agents.—Other non-specific agents are used occasionally. Milk given subcutaneously in small doses (0.5 cc. to 3 cc.) has been advocated by Schiff.[37] Several so-called asthma remedies consist of whole milk, or fat-free milk, or casein. Milk has also been used in large doses to provoke a febrile reaction similar to that obtained with typhoid vaccine intravenously, with consequent temporary cessation of attacks. Sulphur given subcutaneously as a non-specific agent has been recommended by Storm van Leeuwen.[38] Henske claimed good results with autohemotherapy. Organ extracts and vaccines form the basis of some proprietary remedies. All of these non-specific agents have been given with more or less success and are often quite useful when the underlying cause of paroxysms has not been determined or in intractible cases where even temporary relief will allow a patient to regain sleep and strength.

ROENTGEN-RAY THERAPY.

Roentgen-ray therapy of bronchial asthma has developed in recent years. This treatment was based largely upon the observation of Drey and Lossen[39] who treated a patient suffering from leukemia and coincident asthmatic attacks with roentgen-rays. The asthma which had been present for years became better, although the radiation had been applied to the spleen. Soon thereafter, several series of cases of bronchial asthma treated with radiation to the spleen were reported.[40,41,42] In the main, this treatment met with

encouraging success, and complete cessation of attacks in long-standing asthma was recorded in many cases, and marked improvement occurred in many others. Eimer[43] applied roentgen-rays to the chest, and Gerber[44] combined the two methods, radiating the front and back of the chest and the front of the spleen. His method is to use 10 per cent to 15 per cent of a skin erythema dose at each exposure with a ray of short wave length (170 200 Kv.) through a filter of 0.5 mm. copper with 1 mm. aluminum. His target distance is 50 cm. An area of 8 square inches of skin is exposed. Each area is treated on separate days with a day of rest between.

Many theories have been advanced as to the mechanism by which asthmatics have been relieved by roentgen-rays. Pohlmann's[45] conception was that the spleen shares in the production of certain antibodies. He recalled that the function of antibody production has been shown to be taken up by the liver and bone-marrow and actually enhanced in splenectomized rabbits. There is some experimental evidence that radiation will prevent anaphylactic shock in sensitized guinea-pigs as shown by Hajos.[46] Moncorps[47] has demonstrated that after splenectomy there is a marked rise of eosinophiles in the blood of guinea-pigs and since these cells are believed to take part in the destruction of foreign proteins, it is conceivable that they add to the defense against such invading substances. However, this rise does not take place for quite some time after splenectomy and, therefore, could not explain the immediate beneficial effects of roentgen-rays. Müller[48] noted a rapid decrease in blood eosinophiles in asthmatics treated with radiation and believed this coincident with relief. As pointed out elsewhere, however, eosinophiles act within the tissues and a blood eosinophilia is not necessarily an index of the numbers present in the body.

Other suggestions as to the mechanism of roentgen-ray therapy in asthma have been made; such as its action on the

lymph nodes at the hilus of the lung and consequent release of pressure on the bronchi,[44] and also that its effect is possibly merely an expression of psychotherapy. Whatever the true explanation may prove to be, a certain number of cases of asthma do seem to improve under radiation although, at best, the proportion is small. If other measures fail, however a trial with roentgen-rays is indicated.

SURGICAL MEASURES.

The surgical treatment of asthma was confined to the nose and throat until recent years. The successful relief of many cases of angina pectoris by neurosurgery led to a consideration of applying similar procedures to asthmatics. Kümmel[49] in 1923 was the first to perform such an operation, and he extirpated the superior, middle, and inferior cervical sympathetic ganglia with good results in 3 cases. Thereafter, a number of similar operations were reported, with encouraging effects. The largest series was performed by Witzel[50] who performed cervical sympathectomies usually of the stellate ganglia on the right side on 40 asthmatics. The relief of paroxysms thereafter was pronounced. Kappis[51] was the first to sever fibers of the vagus for the relief of asthma and his results were quite as striking as in those cases in which sympathectomies were performed. It is difficult to conceive how each of these operations could meet with equal success, especially in view of the fact that, insofar as is known, bronchoconstriction from nerve stimulation is a function of the vagus solely. Conversely, dilatation of constricted bronchioles is accomplished by stimulation of the sympathetics. Theoretically sympathectomy should deprive the vagus of sympathetic control which in turn should increase the tendency to bronchospasm. It is quite likely, as Kümmel pointed out, that the explanation lies in the probable anatomical arrangement of the vagus and sympathetic fibers. It is known that there is an intimate interweaving of these filaments in the pulmonary plexus, and some vagus fibers,

particularly those controlling the bronchial musculature, may be carried to the stellate ganglion. Extirpation of this node would, therefore, cause a vagus block. Other theories have been advanced which involve a presumable bronchoconstrictor center, and also the assumption that the effect of any such operation is purely psychical. Until the neuroanatomy of these parts becomes understood more clearly, there can be no adequate explanation of the beneficial effect of sympathectomy on bronchial asthma. The influence on both lungs of unilateral interference also requires further study although, as has been pointed out elsewhere, there is evidence of some crossing of bronchoconstrictor fibers of the vagus. These operations have been performed usually in cases of long-standing asthma and have not found much favor in this country. Kern[52] has reported one case wherein the right vagus was severed with but temporary relief.

PSYCHOTHERAPY.

Psychotherapy in asthma has long been practised, inasmuch as asthma has been considered a nervous affliction almost since its recognition as a disease entity. Psychoanalytic methods, hypnosis and other forms of suggestive treatment have been employed. It is important to recognize that asthmatics are often nervous individuals and that asthma is thought to be a nervous affliction by many of the laity. Occasionally cases are encountered wherein attacks are induced by excitement and emotional stress. In these instances, the services of a competent neurologist who will consider each case in terms of its particular underlying psychical factors, are often of great assistance; far more so than sedative drugs.

TREATMENT OF COMPLICATIONS.

There remains to be considered the treatment of direct complications of asthma, most of which have been detailed above. The most important is chronic bronchitis, for statis-

tically this sequela is quite constant and once it is well established, its treatment is difficult and discouraging. Consequently, its prevention is essential and this is accomplished by unremitting efforts toward the relief of asthma in its early stages. Once bronchitis has set in, sinus disease should be sought for and treated adequately. Inasmuch as bronchitis is usually worse in the winter months, climatic treatment is often very beneficial. In the dry even climate of Arizona, these cases do quite well. Likewise, Florida is a good place for such patients in the winter months. In California, on the other hand, especially on the coast, the changes in temperature at night are apt to be too great and these patients do better farther inland. Autogenous vaccines made from sputum when pure cultures of pathogenic organisms are found, are sometimes of value. Bronchiectasis when extensive, should receive postural drainage, pneumothorax or cautery pneumectomy when indicated, and it is surprising how well asthmatics tolerate these procedures.

For emphysema, when advanced, the same treatment as that for bronchitis with which it is usually associated is indicated.

Although the heart in all probability does not suffer from the effects of asthma, cases are seen to improve with rest in bed in a hospital and with digitalis. It is a matter of considerable question whether the beneficial effects in these patients is due to cardiac treatment, for, as has been observed, so many patients, even those in whom there is no suggestion whatever of cardiac failure, lose their attacks under these circumstances. This improvement may reasonably be attributed to changes in environment for often the same treatment at home is without benefit.

From the foregoing, it becomes evident that there is no prescribed treatment for all asthmatics. With some understanding of the underlying principles involved, each case must be considered as an individual problem. In general, successful treatment of this disease is in proportion to the

amount of unremitting intelligent effort spent upon it. Prevention of complications implies early treatment and it is just these cases that offer the greatest opportunities for relief. Once this is accomplished, patients usually can be kept under control. But as the disease is based primarily on an underlying constitutional defect, the liability to recurrence, although tending to decrease as the years of life advance, is always present. At best, the treatment of bronchial asthma is discouraging. However, the conception of this disease which has been revealed during the past decade has contributed more toward its relief than all the knowledge of it during the preceding centuries. It is this advance and the new and widespread interest in this malady that offers encouragement for the future.

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APPENDIX.

DIAGNOSTIC METHODS.

SKIN TESTS.

By far, the most important diagnostic procedure in bronchial asthma is the skin test. The success of this depends upon the potency of the material used for testing, and the interpretation of the reactions obtained. There are two methods employed and each has its advantages.

The cutaneous, or scratch test, is the more widely used because its performance is simpler than the intradermal method. It was developed largely by Walker and depends on the solution of powdered allergens over a superficial scratch of the skin. The dry material is easy to handle and keeps its potency for a considerable length of time. The scratch is so superficial that only moderate aseptic precautions become necessary. Other than a little practice to attain scratches of a proper depth, the test offers no difficulties. Inasmuch as it is less sensitive than the intradermal method, it gives fewer false positive reactions. Finally, the scratch method is more comfortable to the patient.

The interdermal method consists of the introduction of a sterile extract of the allergen to be tested just beneath the superficial layers of the skin. This causes a small wheal, and when the reaction is positive, a larger wheal results, so that some experience is necessary to determine the degree of response. The equipment required for this test includes a rather large number of sterile syringes and needles.

A comparison of the effectiveness of the two methods is unquestionably in favor of the intradermal test. This was adequately shown by Brown[1] and by Larsen and his associates.[2] They found that when both methods were used on

the same individual at the same time, about 50 per cent more positive reactions were obtained in a series of cases with the intracutaneous test than with the scratch method. This compels the routine use of the intradermal method of testing, despite the fact that it is the less convenient procedure.

Allergens for use in testing are supplied by several commercial concerns. If any considerable amount of these substances is to be used either for diagnosis or for treatment, it is more satisfactory and economical to prepare them, especially those for intradermal use. The exact strengths of the extracts, thereby, are known and their cost is relatively inexpensive.

The collection of material for the preparation of extracts offers no particular difficulties, excepting the pollens. Foods are obtained in a state as pure as possible; animal emanations are collected directly, such as currycombings from horses; and some may be purchased, such as raw feathers or wool. Pollens that are quite pure may now be bought. This new industry has recently been established and several concerns collect and market these pollens for extraction, which exemplifies how widespread the treatment of hay-fever has become. This is a great convenience and obviates a laborious process which previously had to be undertaken. There are several methods of pollen collection, all of which depend upon bringing the plants into draught-free rooms and catching the pollens as they shed.

The allergenic fractions of most substances are soluble in physiological saline solution and this solvent was used in the earlier methods of extraction. It proved to be not entirely satisfactory, however, as many preparations thus made deteriorated rather rapidly, and certain others were of low potency at best. Based upon the fact that many allergens reach the mucous membranes in a dry state, Coca[3] assumed that their solution was enhanced by the slight alkalinity of the body fluids. After considerable experimentation, he prepared a solvent containing sodium chloride, and sodium

bicarbonate, with phenol to maintain sterility. He since has modified this by the use of a buffered saline solution which was described by Alice Evans.[4] Its composition is as follows:

KH_2PO_4	3.63 gms.
Na_2HPO_4	14.31 gms.
NaCl	50.0 gms.
Distilled water to	1000 cc.

This is kept as one stock solution, and a 4 per cent phenol solution in water as another. Equal parts of these two stock solutions are mixed and 1 part of this mixture is added to 4 parts of distilled water, which makes the final dilution for the extraction of essentially all dry materials, and is used also as a diluting fluid. When fruits and many vegetables which contain large amounts of water are prepared, the solvent of a concentration five times as great as that ordinarily employed is used, in order to prevent too great a final dilution.

Many substances, such as the epidermis of animals; nuts, and pollens, contain an oily substance which may prevent adequate contact with the extracting fluid. It is removed by treatment with ether, which does not extract allergenic fractions.

Certain materials, such as powders, feathers and the separation of fractions of egg, require special treatments, all of which are described in Coca's excellent directions. A description of the extraction of the allergenic portion of horse dander, will serve as an example of the procedures involved in the preparation of a typical allergen.

A quantity of dander obtained by currying and containing few hairs is mixed with 3 volumes of ether by stirring. After the sediment has completely settled, the ether is decanted and discarded. The material again is extracted with another equal portion of ether. The ether is then completely removed from the sediment by stirring the latter in a beaker immersed in hot water. Fifty grams of the resultant material are mixed with 100 cc. of toluol and then with 1000 cc. of extracting

fluid (described above). The mixture is allowed to stand overnight in a stoppered flask. During this period the mixture is shaken once. On the following morning the entire mixture is filtered through a hard paper. About 800 cc. of a clear brown filtrate are thus obtained. This is immediately filtered through a Berkefeld filter. A Kjeldahl determination for the nitrogen content of the clear filtrate then may be made, and the filtrate diluted with sterile extracting fluid to any desired strength for a stock extract. Finally, the material is cultured both aërobically and anaërobically to determine sterility. In a later article, Coca[5] advises a period of forty-eight hours or longer for extraction, and dialysis is carried on at room temperature for six days against the same fluid that is used for extraction.

The preparation of dried allergens for the scratch test is more laborious than of the extracts. This has been described by Wodehouse.[6]

For intradermal tests, the extracts are best put up in 15-cc. vials capped with "no-air" rubber stoppers of which the plugs have been cut off. The caps are swabbed with iodine before use. These vials are set in a wooden tray with holes bored to contain them, and are labeled and arranged in constant order. The most convenient syringes are the blue-barreled tuberculin type with the Luer adapter, of 1-cc. capacity and graduated in hundredths of this amount. Luer needles 25 or 26 gauge are the most useful. After sterilization by boiling or by soaking in alcohol for ten minutes and then thorough rinsing in sterile physiological saline solution, the needle is plunged through the cap of the vial and the extract drawn up into the syringe. Two one-hundredths of a cubic centimeter is injected for each test. If several tests with the same extract are to be done, the vial is tapped but once and the needle changed for each injection. In order that a series of injections into an individual may be read at one time, it is better to load all the syringes first. Pen-holders made of wire wound in a spiral are very convenient

to hold the loaded syringes, and it is well to keep them in a constant order.

The site of injections should be constant. The outer aspect of the arm between the elbow and insertion of the deltoid is convenient. The forearm is used frequently but the wheal raised by the injected fluid tends to be larger here, especially so near the elbow as shown by Larsen and his co-workers. Hence, positive reactions are more difficult to determine. The skin is sterilized with alcohol, and the needle inserted just beneath the skin. It is well to space injections about an inch apart so that if positive reactions be pronounced they will not "run" into each other. Also, it is better not to have injections in vertical lines in order to permit adequate lymphatic drainage from each wheal.

Reactions if positive are usually fully developed within fifteen or twenty minutes. They appear as raised wheals of a yellowish-pink color with irregular outline or "pseudopods," surrounded by an erythematous zone. These vary in size from a wheal slightly larger than the non-reacting wheals to one several centimeters in diameter. Their interpretation becomes a matter of experience, but it is a safe rule to regard as positive only those that are unquestionably so, although doubtful reactions should be repeated at some other time. Skins vary as to their reactions to irritants and all wheals formed by injections usually increase somewhat in size. Occasionally, dermatographic skins will respond to the injections so vigorously that testing no longer becomes feasible.

The scratch test is best done with a sharp scalpel or with a safety-razor blade. The anterior surface of the forearm is the most convenient site for these tests, as the droplets are best held in place here. It is important that the scratch be very superficial and no blood be drawn. Each scratch should be of about the same length and depth and each is then covered with a drop of $\frac{N}{10}$ sodium hydroxide solution from a dropper with a rubber bulb. An amount of powdered

allergen sufficient to cover the end of a flat sterilized toothpick which is inserted into the vial, is used. The allergen is rubbed into the solvent over the scratch until it is essentially dissolved. After about twenty minutes, the solutions are washed off the forearm and any wheals noted. These simulate those which are obtained by the intradermal method but, as a rule, are not as large.

Not infrequently, very pronounced reactions are encountered. The wheal becomes very large and the lymphatics which drain the area appear as red streaks running up the arm. The site of reaction then grows red, swollen and hot. In these instances, general reactions may follow unless precautions are taken. If the reacting wheal develops very rapidly, a tourniquet drawn sufficiently tight to constrict the superficial lymphatic channels, and yet not interfere appreciably with the radial pulse, should be placed just above the site of the tests to help check systemic absorption. Cold compresses are then applied locally and 0.5 cc. of epinephrine solution injected subcutaneously into the opposite arm. If general symptoms develop in spite of these measures, the same dose of epinephrine should be repeated. Very occasionally it must be increased. These symptoms of a general reaction appear somewhat as follows: The face becomes suffused and an angioneurotic edema and generalized urticaria may develop. The eyes itch and the conjunctivæ redden as in hay-fever. The nose may become stuffy and a tightness felt in the chest which occasionally develops into an asthmatic paroxysm. There may be, also, gastro-intestinal colic, vomiting and diarrhea. In extreme cases, violent asthma, laryngeal edema, cyanosis and asphyxia appear. Occasional deaths have occurred. Broughton[7] has reported such a case, wherein an individual hypersensitive to horse serum, was given a single drop of this intravenously. Death occurred shortly, and postmortem findings showed some lesions typical of bronchial asthma.

The ophthalmic test is performed by placing a drop of a

weak solution of an allergen on the conjunctiva. A positive reaction when slight is indicated by a reddening about the inner canthus. More severe responses are seen as a scleral hyperemia and the eye becomes markedly bloodshot. The advantage of the test lies in the fact that a mucous membrane connected with the upper respiratory tract is thus exposed, and a positive reaction may be obtained in the absence of skin sensitivity. On the other hand, but one solution may be used and strong reactions are both uncomfortable and disfiguring. This test was one of the earliest used for the detection of hypersensitiveness.

Recently, as has been stated, allergy to certain substances may be demonstrated by means of atropic reagins. The blood serum of a hypersensitive individual is secured under sterile precautions and injected into a normal skin. After some hours the cells about the site of injection become passively sensitized to the allergen to which the donor is hypersensitive. On injecting an extract of this allergen at the place where the serum had been introduced, a typical wheal develops, whereas injection of the same extract at a point removed invokes no reaction. The test is of value when the usual skin tests are not feasible, as in infants, nervous patients or in the presence of interfering skin lesions. Under these circumstances, the serum of the patient is injected at several sites into a normal skin and injections of the extracts of the allergens to be tested for, is made later at these places.

SPUTUM EXAMINATION.

One of the most important diagnostic procedures in bronchial asthma is an examination of the sputum for the presence of spirals and of eosinophiles. The character of the sputum identifies the disease. In the gross, it is best studied when collected in a Petri plate and then held against a black background. In cases uncomplicated by chronic bronchitis, little grayish-white specks are seen in the mucoid mass.

These perles are ravelled spirals. The sputum is very sticky and is best handled by placing it in a wide-mouthed bottle of about 30-cc. capacity, a little more than half filled with sterile physiological saline solution. The bottle is tightly corked and shaken vigorously. The sputum then begins to fragment, and the perles uncoil partially and appear as short fine white threads which may be isolated readily with a loop, and examined beneath a cover-glass under the low power of a microscope. The typical spiral is thus identified. Under higher power, it is found to enmesh eosinophiles and sometimes bacteria, or flakes of powder which may have been burned and inhaled for relief of symptoms. If such a spiral be wiped across a glass slide which is then stained by Wright's method, eosinophiles may be shown clearly. When chronic bronchitis is present, perles are somewhat more difficult to identify, but they usually persist.

When a culture of asthmatic sputum is desired, the same process is undertaken, excepting that the isolated spirals, or larger mucous threads when present, are passed through one or two washings and then drawn directly across blood-agar plates. In this way, not only are mouth organisms largely eliminated, but the bacteria in the spirals and, thus, presumably, from the bronchioles, are available. Under these circumstances, cultures often reveal a small to a moderate growth of some one organism which predominates.

ROENTGEN-RAYS OF CHEST.

Roentgen-ray studies of the lungs of asthmatics are interesting but positive findings occur only after bronchial infection has occurred. Early in the course of the disease, the lungs appear essentially normal. The early changes include a widening of the hilus shadows from which markings radiate laterally. These indicate bronchial or peribronchial thickening. It is surprising how early in the disease this may occur. As the disease progresses, these markings extend toward

the periphery in all directions until finally there are wide fan-like markings over the entire lung fields. At this stage, emphysema is usually pronounced, and the diaphragmatic shadows are low and tend to become flattened and are often irregular from adhesions. The emphysema and consequent hyperventilation will often appear as darkened areas, especially over the lower lobes and partially obscure the bronchial markings. Hence, these exposures should be made with a lessened time interval. Not infrequently a mottling is seen which probably represents secretion. The reports on chest films from asthmatics frequently record the diagnosis of pulmonary tuberculosis. The large amount of scarring makes the interpretation of a possible attending tubercular lesion difficult. It must be borne in mind that the oft-quoted impression that asthma and pulmonary tuberculosis rarely are concomitant, has been refuted quite amply.

Essentially no observations are available concerning the roentgen-ray picture of the lungs during an asthmatic paroxysm. A few such films observed by the author in early cases show nothing more than signs of emphysema.

Roentgen-ray pictures of the heart in bronchial asthma show, as a rule, no enlargement. Usually the cardiac shadow is elongated due to the attendant emphysema with a consequent descent of the diaphragm. There is, therefore, a pull on the pericardial attachment with a lengthening of the vertical diameter and a decrease in width of the heart shadow.

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